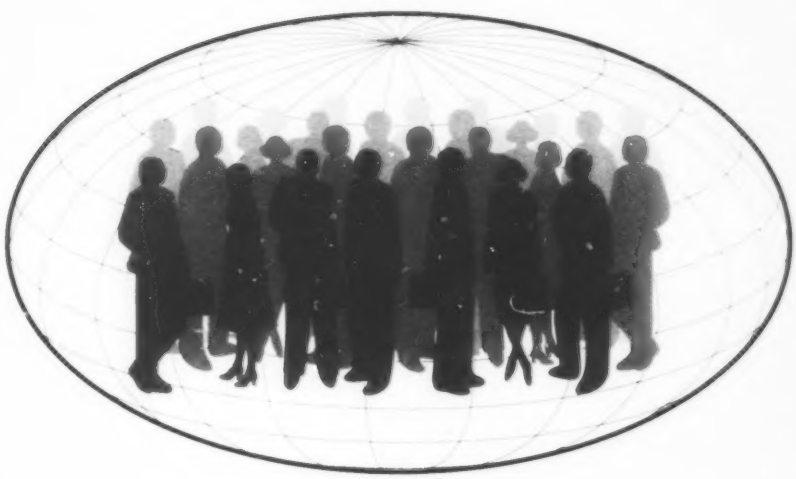
Symposium on

LEUKEMIA CLUSTERING

Ottawa, Canada
March 11, 1992

Proceedings



Co-sponsored by

Advisory Committee on Radiological Protection, AECB
AECL Research Company
Atomic Energy Control Board
Health and Welfare Canada

Edited by

V. Elaguppillai, J.P. Goyette, G. Hill,
D. Krewski and R.V. Osborne

Atomic Energy Control Board | Commission de contrôle de l'énergie atomique

Canada

SYMPOSIUM ON

LEUKEMIA CLUSTERING

Ottawa, Canada
March 11, 1992

Proceedings

Co-sponsored by

Advisory Committee on Radiological Protection, AECB
AECL Research Company
Atomic Energy Control Board
Health and Welfare Canada

Edited by

V. Elaguppillai, J.P. Goyette, G. Hill,
D. Krewski and R.V. Osborne

Published by
Atomic Energy Control Board, Ottawa, Canada
July 1992

93-01589

To obtain additional copies, please contact:

Atomic Energy Control Board
P.O. Box 1046, Station B
Ottawa, Ontario, Canada K1P 5S9

Telephone: (613) 995-5894
Fax: (613) 992-2915

Les actes du symposium sont également disponibles en français.

TABLE OF CONTENTS

Page

Preface v

Programme of Symposium 1

Opening Address — R.J.A. Lévesque 3

Objectives of the Symposium — R.V. Osborne 5

Statistical Methods in Cancer Research: Investigating Localized Clusters of Disease — P. Boyle and F.E. Alexander 7

Non-Traditional Inheritance — J.G. Hall 9

A Review of the Epidemiological Studies of Leukemia Clusters in the United States — C.W. Heath 11

A Review of the Epidemiological Studies of Childhood Leukemia around Nuclear Facilities in the United Kingdom — G.J. Draper 13

Childhood Leukemia in the Vicinity of Nuclear Power Plants in Germany — B. Grosche 19

A Review of Epidemiologic Studies of Childhood Leukemia in Canada — J.R. McLaughlin 25

Chemical Exposure and Leukemia Clusters — R.A. Cartwright 27

Discussions 31

Concluding Remarks 35

Glossary 39

List of Participants 44

PREFACE

Clusters of leukemia* in populations living in specific locations in various countries have been examined by scientific and medical experts for many years. In general, the reason for the existence of these clusters is unknown. The recent discovery of a small cluster of leukemias among children who were born in the vicinity of a nuclear fuel reprocessing facility in England has stimulated wide interest in the possible occurrence of clusters of leukemia around nuclear facilities. Support for a one-day symposium on leukemia clusters was provided by the Advisory Committee on Radiological Protection of the AECB, AECL Research, the Atomic Energy Control Board, and National Health and Welfare Canada. The purpose of this symposium was to present scientific evidence concerning the existence of leukemia clusters in the population, to discuss possible causes for these clusters and to suggest directions for future research. Distinguished speakers from Canada, the United Kingdom, Germany, Italy and the U.S.A. participated in this symposium which was held in Ottawa on March 11, 1992.

The proceedings of the symposium are given in this volume.

The Programme Committee was composed of the following persons:

V. Elaguppillai, Atomic Energy Control Board

J.P. Goyette, AECB Advisory Committee on Radiological Protection

G. Hill, National Health and Welfare Canada

D. Krewski, Health and Welfare Canada

R.V. Osborne, AECL Research Company

Transcriptions of the taped discussions and concluding remarks were provided by D.K. Myers under contract to the Atomic Energy Control Board.

---

* For consistency, the spelling of "leukemia" has been used throughout these proceedings, except in official denominations of organizations and bibliographical references, as appropriate.

SYMPOSIUM ON LEUKEMIA CLUSTERING

Ottawa, Ontario
March 11, 1992

PROGRAMME

Session 1	**Chairperson: Richard V. Osborne** **(Director, Health Sciences and Services Division, AECL Research Company, Chalk River)**
8:30	*Opening Address* RENÉ J.A. LÉVESQUE (President, Atomic Energy Control Board, Ottawa, Canada)
8:45	*Objectives of the Symposium* RICHARD V. OSBORNE (Chalk River Laboratories, AECL Research Company, Chalk River, Canada)
9:00	*Statistical Methods in Cancer Research Investigating Localized Clusters of Disease* PETER BOYLE (Director, Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy) and FREDA E. ALEXANDER (Director, Leukæmia Research Fund Centre for Clinical Epidemiology, University of Southampton, U.K.)
Session 2	**Chairperson: Brian C. Lentle** **(Chairman, AECB Advisory Committee on Radiological Protection)**
10:20	*Non-Traditional Inheritance* JUDITH G. HALL (Professor and Head, Department of Pediatrics, British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada)
11:00	*A Review of the Epidemiological Studies of Leukemia Clusters in the United States* CLARK W. HEATH (Vice President, Epidemiology and Statistics, American Cancer Society, Atlanta, U.S.A.)
Session 3	**Chairperson: Arthur M. Marko** **(Vice-Chairman, AECB Advisory Committee on Radiological Protection)**
13:15	*A Review of the Epidemiological Studies of Childhood Leukemia Around Nuclear Facilities in the United Kingdom* GERALD J. DRAPER (Childhood Cancer Research Group, University of Oxford, U.K.)
14:00	*Childhood Leukemia in the Vicinity of Nuclear Power Plants in Germany* BERND GROSCHE (Head, Epidemiology and Statistics, Institute of Radiation Hygiene, Federal Office for Radiation Protection, Neuherberg/Munich, Germany)
Session 4	**Chairperson: Dan Krewski** **(Chief, Biostatistics and Computer Applications, National Health and Welfare Canada)**
15:00	*A Review of the Epidemiologic Studies of Childhood Leukemia in Canada* JOHN R. MCLAUGHLIN (Senior Epidemiologist, Ontario Cancer Treatment and Research Foundation, Toronto, Canada)
15:40	*Chemical Exposure and Leukemia Clusters* RAYMOND A. CARTWRIGHT (Director, Leukæmia Research Fund Centre for Clinical Epidemiology, University of Leeds, U.K.)
Session 5	**Chairperson: Mary P. Measures** **(Manager, Radiation and Environmental Protection Division, AECB)**
16:15	Discussions Concluding Remarks

OPENING ADDRESS

René J.A. Lévesque
President, Atomic Energy Control Board
P.O. 1046, Station B, Ottawa, Canada K1P 5S9

Ladies and Gentlemen:

[*Translation*]

It is my great pleasure to welcome you to this symposium on leukemia clustering. I do so on behalf of the four sponsoring organizations of this very important symposium, the Atomic Energy Control Board, its Advisory Committee on Radiological Protection, the Environmental Health Directorate of the Federal Department of National Health and Welfare and the Health Sciences Division of the Chalk River Laboratories of AECL Research Company.

[*English*]

The Atomic Energy Control Board, as the federal regulatory agency, is responsible for the regulation, control and supervision of the development, application and use of atomic energy, and for participation in measures of international control of the use of atomic energy. The Board exercises its control and supervision through the *Atomic Energy Control Regulations*, and these Regulations permit such conditions to be placed on its licensees as it deems necessary in the interest of health, safety and security and protection of the environment. The Board carries out its mission with the help of its staff and its two advisory committees. The Advisory Committee on Radiological Protection consists of individual experts from research and health care institutions, the nuclear industry and academia. The Committee advises the Board, through the President, on matters pertaining to the radiation protection of workers and members of the public, as well as on protection of the environment, against the harmful effects of ionizing radiation arising from its licensed activities. The Health Sciences and Services Division of the Chalk River Laboratories is responsible for developing improved techniques to assess radiation exposures to workers, the public, and the environment; to understand and predict the effects of radiation on the health of humans and the environment; and to provide the tools to improve radiation protection in nuclear facilities.

The responsibilities of the Environmental Health Directorate, part of the Health Protection Branch of National Health and Welfare Canada, include studying adverse effects of the chemical and physical environment on human health, and ensuring the safety, effectiveness and non-fraudulent nature of radiation emitting and medical devices. The Directorate also conducts research on radiation hazards and the adverse affects of environmental chemicals. The problem of the possible geographical clustering of leukemia in the vicinity of nuclear facilities is thus important for all four sponsors of this symposium.

As you are aware, leukemia is one of the many health detriments of exposure to ionizing radiation. But it was not controversial until the investigation, by Professor Martin Gardner, of a cluster of leukemia among children who were born in the vicinity of the Sellafield nuclear fuel reprocessing facility in the United Kingdom. (Unfortunately, Professor Gardner, who was supposed to be here with us today, is unable to make it, owing to medical reasons.)

Although only four children died of leukemia, compared to an expected 0.5, during the 35 years from 1945 to 1980, Gardner's finding sparked a worldwide interest in the occurrence of clusters of leukemia, particularly around nuclear facilities. Fear and suspicion have fuelled the recent debate about whether there is a connection between the excess number of childhood leukemia cases and the nuclear facilities.

In Canada, the Atomic Energy Control Board, on the advice of its staff and of its Advisory Committee on Radiological Protection, decided to sponsor a study to investigate the occurrence of any such clusters of leukemia among children born in the vicinity of major Canadian nuclear facilities. The Board contracted the Ontario Cancer Treatment and Research Foundation to conduct such a study around five different types of nuclear facilities in Ontario. Although the study did not find any significant excess of childhood leukemia around these facilities, the issue of clusters of leukemia has continued to be debated at national and international fora.

The occurrence of diseases in clusters is not something new. From the beginning of the discipline of epidemiology early in the last century, studies of the geographical distribution of the occurrence of communicable

diseases have been an important source of causal hypotheses. Perhaps the most famous is the study by John Snow, who looked at the clustering of cholera in relation to the supply of drinking water in the city of London, England. This famous study led to the eventual control and eradication of cholera and other water-borne diseases in England and elsewhere. The experience gained from the study of the clusters of communicable diseases have led to similar investigations of non-communicable diseases, such as cancer. Since the incidence of cancer, and in particular, leukemia, is very low, and since there is a long latent period for the induction of cancer, the detection of clusters of cancers and the interpretation of the results of such epidemiological studies are usually very difficult. If the number of excess cases is small compared to the number expected of a particular type of cancer, then the question which comes to mind is whether or not such a observed cluster is simply a phenomenon which occurred by chance. Is the cluster an artefact of the statistical methodology, or the result of variability in the reporting of these cancers, or the result of some environmental factor such as radiation, chemical or viral infection, social habits or even genetic predisposition to the disease?

In view of these uncertainties associated with the interpretation of the occurrence of clusters of childhood leukemia, the Advisory Committee on Radiological Protection advised the AECB to organize a symposium on clusters of leukemia, and thereby provide a forum to discuss the state of knowledge of the subject.

I am very proud to say that Canada has been a world leader in the study of radiation-induced health effects. Canadian scientists have participated in national and international scientific committees which have influenced the design and conduct of epidemiological studies, and the application of the results of such studies for setting limits for exposure to ionizing radiation. It is worth mentioning the pioneering work of one of our prominent scientists, Dr. Howard Newcombe, on the record linkage methodology, a technique used worldwide in epidemiological studies. Dr. Newcombe was a scientist at the Chalk River Laboratories of AECL Research Company, a co-sponsor of this symposium. Canadian scientists at Statistics Canada have established a world-renowned national Mortality Data Base and a National Cancer Incidence Reporting System, which are the back-bone of numerous epidemiological studies. The Bureau of Radiation and Medical Devices of the Environmental Health Directorate is the architect of the establishment of a National Dose Registry for radiation workers in Canada. This registry contains the dose information on some 300,000 workers exposed to radiation in their occupational environments. These data bases are considered to be among the best documented in the world, and they greatly facilitate a comprehensive follow-up of the health status of persons exposed to ionizing radiation. Canada has provincial cancer registries which provide the basic information of the national cancer incidence reporting system. I believe that world class scientists, exploiting these databases, will contribute greatly to elucidating the role of radiation in cancer induction, and will also help to clarify the significance of observed clusters of cancers. Another important product of the analysis of these data bases is, of course, better accuracy of risk estimates for radiation exposures.

[*Translation*]

There is no doubt that this symposium is timely. The question of the existence of clusters of childhood leukemia, and their possible causes, is of considerable importance in determining the causes of cancer. This symposium brings together scientists from four countries where this question has been studied. It is our hope that this sharing of experience and ideas will lead to a better understanding of the question.

I look forward to an informative and productive day.

OBJECTIVES OF THE SYMPOSIUM

Richard V. Osborne

Health Sciences and Services Division, Chalk River Laboratories
Chalk River, Ontario, Canada K0J 1J0

One of the duties that I have been asked to undertake in this first session is to remind you of the objectives of today's symposium. We have people here, including our speakers, who are eminent in those areas of science and medicine that bear on our topic. Our objectives should be perhaps regarded as a challenge to our speakers and the other experts.

All of us are aware, I expect, that there has been great epidemiological activity in the last few years on the topic of leukemia clustering. The first objective, then — our starting point — is:

> ***To present and examine the recent evidence associating clusters of leukemia with sources of ionizing radiation.***

In other words — just what evidence is there for the associations?

We can examine this evidence for associations in several ways. Perhaps one of the most important is to test any apparent association against known biology. Are there plausible explanations that could support a causal relationship underlying the associations? Are there other credible explanations? Our focus has been on associations between leukemia and exposures to ionizing radiation but what about chemical exposures? Are there influences here that will confound the examination of leukemia and radiation?

We can also ask whether the implications of a postulated causal relationship are consistent with what we know from other studies. For example, what can we say about consistency with the results from the atomic bomb survivors? If there is a simple causal relationship between radiation dose and some effect, what quantitative risk factors can we deduce and what are their uncertainties? Such estimates are needed if we are to have an accurate perspective on any risk. Also, with such a relationship, the occurrences of the effect can be expected to follow the distribution in collective dose. Are the hypotheses for clustering consistent with this?

We might also ask if there are any clues in the observed distribution in time of any observed association. Can postulated explanations account for variations with time?

Another fundamental examination is to ask whether the numbers make sense. We see only a few cases of leukemia, possibly spread over many years. The presence or absence of a single case can make a large change to the strength of an apparent association. Are we trying to get quarts of information out of pint pots of data? What fundamental limitation do the statistics themselves place on any interpretation of the data? We hope, today, as an explicit objective:

> ***To examine the statistical basis for the analysis of clustering.***

I have mentioned the possibility of chemical agents confounding an analysis with respect to ionizing radiation. Implicit in what I was saying was the idea that if the association did not indicate a causal relationship with radiation then the cause must have been an environmental chemical. But we might well ask whether the explanation is more biological. I expect many of you will have seen Kinlen and Hudson's recent paper in the British Medial Journal that adds support to their theory that the transmission of infection in new towns in rural areas can lead to local increases in leukemia. This is an intriguing hypothesis that is biologically plausible. Are there more? Today, therefore, we add a third objective:

> ***To examine the underlying assumption in epidemiological studies that clusters must have an environmental cause.***

Given the data we now have, which explanation would survive Occam's razor?

Keeping biology in mind, we can go on to ask whether the concept of an appropriate control cohort in an epidemiological study is achievable in a biological sense. Can we really say what is expected when we calculate the observed to expected to get an SMR? Paul Unrau and his colleagues at Chalk River are always reminding me that

epidemiological studies rarely consider genetic differences between cohorts, differences that may cause much greater variations in cancer incidence than do environmental factors. There are well-characterized genetic syndromes known to increase cancer incidence, including that of leukemia. Many individuals may be carriers of these genetically-determined traits. People do not mate randomly — so that the frequencies of these genes in local population sub-sets, and hence the frequency of disorders, can be very different from frequencies in the whole population. Therefore, the argument goes, we would expect these non-random breeding patterns to result in non-random risk distributions and in localized variations in cancer incidences. In other words, we should address the role of consanguinity in clusters.

Another of our objectives is therefore:

> ***To examine the extent to which we can take into account the biological causes of non-randomness in populations, particularly those of geographic and genetic origin.***

I suspect that by the end of the day we shall not have a definitive set of answers. And like all scientists who carry out contract work we shall end by saying "further work is needed". It behooves us though, to suggest what that work should be. How are we going to get the answers? In terms of epidemiology we can set out 1other objectives:

> ***To evaluate the relative merits of different kinds of epidemiological studies for yielding significant information concerning clustering; and***
>
> ***To consider the potential utility of combining the results from existing studies, and whether new epidemiological studies might be helpful and, if so, of what kind.***

Given some of the caveates on the application of conventional epidemiological studies to clustering phenomena we have to ask ourselves about the alternatives. Our final objective, then, should be:

> ***To consider what other directions, including application of the technologies of molecular biology, are likely to help clarify the underlying mechanisms or causes.***

In other words, can we take advantage of increasing capabilities to probe the genetic makeup of individuals and to examine the associations between cancer incidence and inheritance directly at the level of the individual?

I said the objectives were challenges; challenges that have to be dealt with if we are going to arrive at a definitive view of leukemia clusters. Having cast the gauntlet, I will step back and let the discussions proceed.

STATISTICAL METHODS IN CANCER RESEARCH: INVESTIGATING LOCALIZED CLUSTERS OF DISEASE

Peter Boyle

Director, Division of Epidemiology and Biostatistics, European Institute of Oncology
Via Ripamonti 332/10, 20141 Milan, Italy

Freda E. Alexander

Director, Leukæmia Research Fund Centre for Clinical Epidemiology,
University of Southampton, Southampton SO9 4XY, U.K.

The search for "clusters" of cancer cases has been a major feature of epidemiological research during the last decade, whether this be a search for aggregations of cases within families, within factories or in geographic terms. The investigation of geographic clusters has attracted the attention of the general public, particularly at a period when there is growing awareness of environmental matters in many countries. Much of the recent activity in this whole area of research has its origin in a television programme made by Yorkshire Television in the United Kingdom, which highlighted the situation of children's leukemia in villages around the nuclear reprocessing plant of Windscale (now Sellafield) in West Cumbria in the north of England. Increasingly, community groups are seeking technical assistance in evaluating and investigating apparent cancer clusters in their community. Similarly, there is frequently community pressure to investigate adverse health effects around point sources such as chemical plants, nuclear plants and waste disposal sites. This pressure has invoked the continuing and growing interest of Public Health departments and other epidemiological groups in investigating disease clustering and disease clusters. In a surprisingly large number of instances, these studies have concentrated on leukemia and, specifically, on leukemia in children.

The history of investigation into leukemia clusters dates back to the early years of this century and is peppered with controversy regarding the role of chance in the occurrence of clusters. The situation is complicated by a lack of the biological insight necessary to decide what kind of patterns to look for.

The result was the use of such a variety of analytical methods that it is difficult to synthesize or even compare the results from many of the earlier studies. Recently, more modern methods have been developed to investigate disease clustering. With the current high levels of interest in disease clustering among many diverse groups and amid continual pressure to examine large datasets for evidence of clustering, it seems important and timely to evaluate the performance of characteristics of the various clustering methodologies.

Clustering is a poorly defined concept and an adequate definition is extraordinarily difficult. It is important to distinguish between the notion of an individual cluster, corresponding to an excess number of cases in one small area or around a point source, and between the general tendency for clustering by which is meant a more heterogeneous "clumped" distribution of cases of disease than would be expected from the variation in population density and chance fluctuations. While precise mathematical models can be formulated from these concepts, these are generally too inflexible to encompass the full range of possibilities seen in practice.

Modern methodological developments have involved two distinct methods: *quadrat counts* [Potthoff and Whittinghill (1966), Urquhart and Black (1988)] and *distance methods* [Cuzick and Edwards (1990), Openshaw (1987), Besag (1989)].

To investigate the comparative performance of these methods, fifty datasets were generated based on various clustering scenarios for childhood leukemia in Yorkshire. The five groups who developed these methods were asked to interpret each dataset in a blind manner. All methods had reasonable success in detecting randomness but all had false positives and false negatives.

It was generally difficult to locate clusters particularly if the location was within or in close proximity to an urban conurbation.

Statistical methods can indicate (with some error) whether clustering is present but cannot tell whether it is "real", i.e., whether cases are related to each other through some social or biological mechanism or through having a common relationship to some other event or circumstance. It can be concluded that, despite limitations to the methodologies and the underlying data (particularly population-at-risk), investigations of clusters represent one of many tools for hypothesis generation and refinement but that new putative causes will always require further, more specific studies before the results become meaningful.

REFERENCES

Cuzick, J. and Edwards, R., "Spatial Clustering for Unhomogeneous Populations (with discussions)", *Journal of the Royal Statistical Society*, 1990, Vol. 52, pp. 73-104.

Besag, J. and Newell, J., "The Detection of Clusters in Rare Diseases", *Journal of the Royal Statistical Society*, 1991, Vol. 154, pp. 143-155.

Openshaw, S., Charlton, M., Craft, A.W., and Birch, J.M., "Investigation of Leukæmia Clusters by the Use of a Geographic Analysis Machine", *Lancet*, 1988, Vol. i, pp. 272-273.

Potthoff, R.F. and Whittinghill, M., "Testing for Homogeneity. II – The Poisson Distribution", *Biometrika*, 1966, Vol. 53, pp. 183-190.

Urquhart, J., Black, R., and Nust, E., "Exploring Small Area Methods", in *Methodology of Enquires into Disease Clustering*, London, Small Area Health Statistics Unit, 1991.

NON-TRADITIONAL INHERITANCE

Judith G. Hall

Professor and Head, Department of Pediatrics, British Columbia Children's Hospital,
University of British Columbia
Vancouver, British Columbia, Canada V6H 3V4

In the last few years a number of non-traditional forms of inheritance has been recognized. These include mosaicism, cytoplasmic inheritance, uniparental disomy, imprinting, amplification/anticipation and somatic recombination. Many of these present mechanisms whereby mutations may manifest in unusual ways which have not been predicted by traditional forms of inheritance. In addition, the possibility of transgenerational affects seems likely.

Genomic imprinting is the observation that phenotype depends on the sex of the transmitting parent. It has been recognized on many different lines of research:

(1) pronuclear transplantation;

(2) triploid phenotypes;

(3) chromosomal deletions;

(4) uniparental disomy;

(5) transgenic mouse work;

(6) childhood cancers; and

(7) single gene disorders.

The mechanism involved in parent of origin affects is likely to have some major affect during meiosis. Observations with parent of origin affects include:

(1) mutation rates;

(2) recombination rates;

(3) chromosome condensation;

(4) imprinting;

(5) late replication; and

(6) chromosome pairing.

It seems possible that each of these processes involve particular areas of chromosomes which are more or less susceptible.

The genomic imprinting phenomenon in humans seems to involve growth, behaviour and, *in utero*, survival. The only human gene which has been demonstrated to have parent of origin affects thus far is insulin-like growth factor type II in which only the paternal protein is expressed while only the maternal receptor is expressed. Parent of origin affects are also seen in childhood cancers, suggesting that all the growth factor genes which have the potential to become oncogenes must be examined for this type of affect. Further, there appear to be tissue-specific parent of origin affect such that, for instance, the retinoblastoma gene has a parent of origin affect in bone but not in the eye while the mutation rate does have a parent of origin affect in the eye.

The mechanism of genomic imprinting is now known. However, it appears that some process is involved in functionally turning a gene off. It would appear that there may be two genes involved therefore in the process; one which produces the product that turns the gene off (the imprinting gene) and the gene itself which is turned off (the imprintable gene). The process of imprinting (functionally turning the gene off) may be associated with methylation, although the initiating event is not known. It is quite clear, however, that erasure of imprinting can occur and this seems most likely to in some way be associated with meiosis.

Imprinting affects can be manifested in a pedigree in such a way as to look like dominantly inheritance, recessively inheritance or multifactorial inheritance. Thus they allude the usual type of genetic analysis of pedigrees.

Interactions between mosaicism and imprinting are thought to occur and in particular have been observed in monozygous twins. In addition, somatic recombination may lead to uncovering imprinting or producing functional hemizygosity.

REFERENCES

"Imprinting Makes an Impression" [Editorial], *Lancet*, 1991, Vol. 338, pp. 413-414.

Haig, D. and Graham, C., "Genomic Imprinting and the Strange Case of the Insulin-Like Growth Factor II Receptor", *Cell*, 1991, Vol. 64, pp. 1045-1046.

Hall, J.G., "Genomic Imprinting: Review and Relevance to Human Diseases", *American Journal of Human Genetics*, 1990, Vol. 46, pp. 857-873.

Hall, J.G., "Nontraditional Inheritance", *Growth, Genetics and Hormones*, 1990, Vol. 6, pp. 1-4.

Hall, J.G., "How Imprinting Is Relevant to Human Disease", in *Development Supplement*, 1990, pp. 141-148.

Hall, J.G., "Genomic Imprinting: Current Opinion", *Genetics and Development*, 1991, Vol. 1, pp. 34-39.

Hall, J.G., "Genomic Imprinting and Its Clinical Implications", *New England Journal of Medicine*, 1992, Vol. 326, pp. 827-829.

Hoffman, M., "How Parents Make Their Mark on Genes", *Science*, 1991, Vol. 252, pp. 1250-1251.

Sybert, V.P., "Mosaicism in Turner Syndrome", *Growth, Genetics and Hormones*, 1990, Vol. 6, pp. 4-8.

Weiss, R., "Uneven Inheritance — A Genetic Quirk Leaves Some People with a Chromosomal Odd Couple", *Science News*, 1990, Vol. 138, pp. 8-11.

A REVIEW OF THE EPIDEMIOLOGICAL STUDIES OF LEUKEMIA CLUSTERS IN THE UNITED STATES

Clark W. Heath

Vice President, Epidemiology and Statistics, American Cancer Society
Atlanta, Georgia, U.S.A 30329

Cancer case clustering first received concerted attention in the United States in the late 1950s. Principal emphasis was on possible viral or infectious causes of leukemia and on childhood leukemia in particular. Between 1960 and 1980, many childhood leukemia clusters were investigated (37 in some detail) by the U.S. Public Health Service's Centres for Disease Control (then the Communicable Disease Centre). Some attention was also given to possible clusters of leukemia at other ages, to clusters of other forms of cancer, and on occasion to clusters of birth defects or of various non-malignant chronic diseases. In no instance was clear evidence established of infectious or environmental causation.

A cluster was defined pragmatically as two or more cases occurring close together, and closeness generally implied joint time-space closeness, although occasionally other parameters applied. Statistical analyses of case distributions in large populations suggested little or no evidence that such clustering occurred among leukemia or cancer cases more often than chance distribution would predict, except perhaps for leukemia in young children.

Detailed investigation of individual clusters focused only on situations with particular evidence of unusual case associations or environmental settings. Over time, such investigations increasingly involved issues of perceived environmental exposures in communities. In several situations ionizing radiation was the principal concern, as, for instance, in communities in southern Utah which were in the path of nuclear test fallout or where uranium ore processing had been a local industry. No convincing links with leukemia occurrence were found.

In 1990, because of growing controversy regarding possible leukemia case clusters in proximity to nuclear facilities in the United Kingdom, the National Cancer Institute published a massive statistical analysis of cancer mortality patterns in counties containing or adjacent to such facilities. Frequencies of leukemia and other cancers in children and adults were compared with data from matched control counties and with the United States as a whole. Mortality data were available for the years 1950-1984, and risk comparisons were made both before and after facility startup, as well as for different groupings of facilities and different age categories. No consistent patterns of increased leukemia or cancer risk were seen among these many comparisons.

This workshop presentation will discuss the evolution of leukemia cluster studies in the United States since 1960. Particular attention will be given to results of the recent NCI national survey and to specific case cluster investigations where questions of radiation exposure were of special concern.

A REVIEW OF THE EPIDEMIOLOGICAL STUDIES OF CHILDHOOD LEUKEMIA AROUND NUCLEAR FACILITIES IN THE UNITED KINGDOM

Gerald J. Draper

Childhood Cancer Research Group, University of Oxford,
57 Woodstock Road, Oxford OX2 6HH, U.K.

1. INTRODUCTION

In this paper we review studies of cancer, especially childhood leukemia, around nuclear installations in the U.K., and relate these to more general studies of geographical variations in incidence and of clustering.

Although there have been a considerable number of reports concerning clusters or increase in incidence around nuclear installations in the U.K., only three sites have been studied in detail: the areas around Sellafield, the site of one of the two U.K. reprocessing plants, and Dounreay, the site of the second, and the area around the two defence facilities at Aldermaston (the Atomic Weapons Research Establishment) and Burghfield (the Royal Ordnance Factory). There have been less detailed studies, and anecdotal reports, concerning other sites. In addition, there have been studies of actual and potential sites of nuclear installations in England and Wales generally.

These reports have stimulated research into statistical methodology for studying possible clusters and clustering and have highlighted the need for investigations into geographical variations in the incidence of childhood leukemia in order to study the possibilities that the observed clusters and areas of high incidence could simply be part of a natural pattern of variation in incidence — though this would still leave unanswered the question of whether cases were more likely to occur in the vicinity of nuclear installations — and why.

In the final part of this paper, we briefly consider data on childhood leukemia and non-Hodgkin lymphomas in Britain over an 18-year period that has been analyzed using a variety of statistical techniques and the possible relevance of these analyses to studies around nuclear installations. These analyses address the questions of whether clustering is a general feature of the incidence of childhood leukemia and whether variations in incidence may be associated with differences in social class or the urban/rural status of an area. A further possibility, briefly considered here, in Kinlen's hypothesis that increases in incidence may be the result of exposure to viruses as a consequence of population mixing.

2. STUDIES AROUND U.K. NUCLEAR INSTALLATIONS

2.1 Sellafield

A reported increase of childhood leukemia in the vicinity of the Sellafield nuclear fuel reprocessing plant in North-West England, and particularly in the village of Seascale which is close to the plant, has been studied in great detail. The initial reports were summarized in the report of a committee chaired by Sir Douglas Black (Black, 1984). Perhaps the most striking of the early reports was one that showed that in the village of Seascale during the period 1956-1983, there were five cases of leukemia in children under 10 years old, resulting in an incidence approximately ten times that expected (Urquhart et al., 1984). The analysis is subject to obvious criticisms concerning the selection of area, age-group and time period. However, more systematic analyses have confirmed the existence, if not the magnitude, of this excess. Gardner and Winter (1984) showed that for leukemia deaths at ages 0-24 in Millom Rural District (the administrative area containing Sellafield and Seascale), there was a four-fold excess in the period 1968-1978 (see Table 1) and a two-fold excess in the longer period 1959-1978.

Gardner et al. (1987a) showed that in Seascale the excess affected those born in this village, and that the excess related not only to leukemia but also to other childhood cancers: among 1068 children born there and followed up for varying periods, there were five deaths from leukemia as compared with 0.53 expected. There was also one non-fatal case of leukemia and an excess of cancers other than leukemia (Table 2). Gardner et al. (1987b) found no excess among 1546 children attending schools in Seascale but not born there (Table 2).

TABLE 1. Leukemia Mortality at Ages 0-24 Near Sellafield
(Gardner and Winter, 1984)

	Observed	Expected	O/E
Ennerdale RD			
1959-1967	3	3.3	0.91
1968-1978	4	3.3	1.21
Millom RD			
1959-1967	1	1.6	0.63
1968-1978	6	1.4	4.35*
			* $p < 0.01$

TABLE 2. Cancer and Leukemia Among Children Born in or Attending Schools in Seascale

	Number of Children	Cancer				Leukemia			
		Deaths		Other Cases		Deaths		Other Cases	
		Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Births	1068	4	1.06	2	1.11	5	0.53	1	0.08
Residents born elsewhere	1546	1	1.50	3	2.01	0	0.54	1	0.03

In a further paper Gardner et al. (1990) reported the results of a case-control study of leukemia and lymphoma among young people in West Cumbria (the area containing Sellafield and Seascale). The most important finding from this study was an association between preconception external ionizing radiation exposure in the fathers (as estimated from monitoring with dose meters worn on the trunk) and the subsequent occurrence of leukemia or non-Hodgkin lymphoma in the children born to these fathers (Table 3). The authors state that "These results seem to explain statistically the geographical association", i.e., the "cluster" of cases at Seascale.

TABLE 3. Leukemia and Non-Hodgkin Lymphomas Below Age 25 in West Cumbria
Paternal Employment and Pre-Conception External Radiation Dose
(Gardner et al., 1990, Table VI)

	Cases	Area Controls	Relative Risk	95% Confidence Interval
Total	66	404		
Father never employed at Sellafield	14	88	1.01	0.51-2.02
Father employed at Sellafield before conception	11	47	1.77	0.82-3.85
Dose record before conception	10	45	1.63	0.73-3.64
Total dose record before conception				
1-49 mSv	4	27	1.06	0.35-3.21
50-99 mSv	2	13	1.16	0.24-5.46
> 100 mSv	4	5	6.42	1.57-26.32

2.2 Dounreay

Around Dounreay, in Scotland, where there is a smaller reprocessing plant, there was an excess incidence of leukemia at ages 0-24 during the 6-year period 1979-1984, but not in the preceding 11 years (Heasman et al., 1986; COMARE, 1988). Again, the magnitude of the excess depends on the time period and area chosen (Table 4).

TABLE 4. Leukemia Incidence at Ages 0-24 Near Dounreay
(Heasman et al., 1986)

	Observed	Expected	O/E
<12.5 km from Dounreay			
1968-1973	0	0.6	0
1974-1978	0	0.5	0
1979-1984	5	0.5	9.75*
12.5 to <25 km from Dounreay			
1968-1973	0	0.5	0
1974-1978	0	0.4	0
1979-1984	1	0.5	2.21
			* $p < 0.001$

The results of a case-control study carried out in Caithness, the area where the Dounreay installation is situated, have been reported by Urquhart et al. (1991). The main conclusions of this study were that the raised incidence around Dounreay "cannot be explained by paternal occupation at Dounreay or by paternal exposure to external ionizing radiation before conception". An association was reported between the use of beaches around Dounreay and the development of childhood leukemia and non-Hodgkin lymphoma, but the authors comment that this association "might be an artefact of multiple testing and influenced by recall bias."

2.3 Aldermaston and Burghfield

For children living near the Atomic Weapons Research Establishment at Aldermaston and the Royal Ordnance Factory at Burghfield in Southern England, an apparent excess of childhood leukemia at ages 0-4 (Roman et al., 1987) and of childhood cancers in the same age-range (Childhood Cancer Research Group data published in COMARE (1989)) has been reported (Tables 5 and 6). The relative risks are much smaller but the numbers of cases involved are considerably larger, since this area of Britain is relatively densely populated. (Again the choice of area raises problems of selection.) A case-control study to investigate these findings is in progress.

TABLE 5. Childhood Leukemia Around Aldermaston and Burghfield

Age	Observed	Expected	Incidence Ratio	
0-4	53	34.0	1.6	$p < 0.01$
5-14	36	35.3	1.0	
Total	89	69.3	1.3	$p < 0.05$

TABLE 6. Childhood Cancer Around Aldermaston and Burghfield

Age	Observed	Expected	Incidence Ratio	
0-4	63	45.7	1.4	$p < 0.01$
5-15	80	70.1	1.1	
Total	143	115.8	1.2	$p < 0.05$

2.4 Nuclear Sites Generally

A report on mortality for all ages and all cancers around nuclear installations in England and Wales (Cook-Mozaffari et al., 1989a) generally found an increase in leukemia mortality at ages 0-24 in districts near to a nuclear installation, although there appeared to be no direct relationship between the magnitude of the excess and the percentage of the population living near the installation; the authors stated that there was no positive evidence that the excess was attributable to population exposure to radioactive discharges. Mortality from leukemia at ages 0-24 was found also to be greater in areas of high social class, but the excess associated with nuclear installations remained when this was allowed for. It may be, however, that the association with nuclear installations arises from an association with some feature of the type of area in which they are situated or the type of population living there. Leukemia mortality at ages 25-64 was significantly lower in districts near installations.

2.5 Potential Nuclear Sites

The possibility that these findings relating to nuclear installations generally are attributable to the type of area in which such installations are situated receives some support from the findings of a second paper by the same group (Cook-Mozaffari et al., 1989b) in which similar results were found for potential sites of nuclear installations, i.e. "sites where the construction of such installations had been considered or had occurred at a later date". For these sites they again found an increase in leukemia mortality at ages 0-24, although this was not significant.

3. STUDIES ON THE INCIDENCE OF CHILDHOOD LEUKEMIA

It is well known that there are quite large international variations in the reported incidence of childhood leukemia (see, e.g., Parkin et al., 1988). Comparatively little is known about variations within a country. Studies have been carried out in the U.K. to investigate the possibility that the results reported around nuclear installations could be part of a general pattern of variation in which areas of high incidence or clusters occur at sites unconnected with nuclear installations (Draper, 1991).

3.1 Geographical Variations in Incidence Generally

Results presented by Stiller et al. (1991) make it clear that there are substantial variations in the incidence of childhood leukemia between areas in the U.K.

3.2 Social Class Differences

In a further series of analyses in the same volume, Draper et al. (1991) found higher rates of childhood acute lymphocytic leukemia in areas of higher socio-economic status (Table 7). Similar findings have been reported previously.

TABLE 7. **Annual Incidence Rates per Million and Socio-Economic Score (Lymphocytic and Unspecified Leukemias)**

Age (in years)	Period	Socio-Economic Score	
		Highest Quintile	Lowest Quintile
0-4	1969-73	53.0	49.6
	1974-78	62.6	50.5
	1979-83	53.4	48.9
5-9	1969-73	28.7	20.5
	1974-78	31.9	28.5
	1979-83	29.7	22.9
10-14	1969-73	14.0	14.5
	1974-78	12.4	13.7
	1979-83	10.2	14.8

3.3 Clusters and Clustering

In a series of other analyses by various authors in the same volume some evidence for a low level of clustering was found.

3.4 Viruses

Kinlen and colleagues in a series of papers (1988, 1990, 1991) have investigated "the hypothesis that leukemia represents a rare response to a much commoner (but unrecognized) infection, the transmission of which is facilitated when large numbers of people come together". This could happen, for instance, if a nuclear installation is built in a previously sparsely populated area. Studies of New Towns and of areas where there was an increase in commuting lend support to Kinlen's hypothesis.

4. CONCLUSIONS

There have been a number of reports of an increased incidence of cancer around nuclear installations in Britain and three of these have been the subject of detailed investigation. Although each of these investigations has produced statistically significant evidence of an increase, there is no coherent and consistent relationship between the results for the three sites, and no hypothesis that will explain them all. In particular, it should be noted that there are very large differences in the magnitudes of the environmental discharges at these sites.

The results that have been studied in most detail are those relating to the vicinity of the Sellafield reprocessing plant; the excess of cases appears to be explained by an association between high preconception doses of radiation among some of the workers and subsequent leukemia or non-Hodgkin lymphoma in their offspring. However, this result would not have been predicted on the basis of current estimates of the genetic effects of radiation.

Finally, it should be emphasized that the numbers of cases involved is very small.

REFERENCES

Black, D., *Investigation of the Possible Increased Incidence of Cancer in West Cumbria*, Report of the Independent Advisory Group, London, HMSO, 1984.

Committee on the Medical Aspects of Radiation in the Environment (COMARE) Second Report, *Investigation of the Possible Increased Incidence of Leukæmia in Young People Near the Dounreay Nuclear Establishment, Caithness, Scotland*, London, HMSO, 1988.

Committee on Medical Aspects of Radiation in the Environment (COMARE) Third Report, *Report of the Incidence of Childhood Cancer in the West Berkshire and North Hampshire Area, in Which Are Situated the Atomic Weapons Research Establishment, Aldermaston and the Royal Ordnance Factory*, Burghfield, London, HMSO, 1989.

Cook-Mozaffari, P.J., Darby, S.C., Doll, R. et al., "Geographical Variation in Mortality from Leukæmia and Other Cancers in England and Wales in Relation to Proximity to Nuclear Installations, 1969-78", *British Journal of Cancer*, 1989, Vol. 59, pp. 476-485.

Cook-Mozaffari, P., Darby, S., and Doll, R., "Cancer Near Potential Sites of Nuclear Installations", *Lancet*, 1989, Vol. ii, pp. 1145-1147.

Draper, G.J. (ed.), *The Geographical Epidemiology of Childhood Leukæmia and Non-Hodgkin Lymphomas in Great Britain 1966-83*, Studies on Medical and Population Subjects No. 53, London, HMSO, 1991.

Draper, G.J., Vincent, T.J., O'Connor, C.M., and Stiller, C.A., "Socio-economic Factors and Variations in Incidence Rates Between County Districts". In *The Geographical Epidemiology of Childhood Leukæmia and Non-Hodgkin Lymphomas in Great Britain 1966-83*, London, HMSO, 1991, pp. 37-45.

Gardner, M.J. and Winter, P.D., "Mortality in Cumberland During 1959-78 With Reference to Cancer in Young People Around Windscale", *Lancet*, 1984, Vol. i, pp. 216-217.

Gardner, M.J., Hall, A.J., Downes, S., and Terrell, J.D., "Follow up Study of Children Born to Mothers Resident in Seascale, West Cumbria (Birth Cohort)", *British Medical Journal*, 1987, Vol. 295, pp. 222-227.

Gardner, M.J., Hall, A.J., Downes, S., and Terrell, J.D., "Follow Up Study of Children Born Elsewhere But Attending Schools in Seascale, West Cumbria (Schools Cohort)", *British Medical Journal*, 1987, Vol. 295, pp. 819-822.

Gardner, M.J., Snee, M.P., Hall, A.J., Power, C.A., Downes, S., and Terrell, J.D., "Results of Case-Control Study of Leukæmia and Lymphoma Among Young People Near Sellafield Nuclear Plant in West Cumbria", *British Medical Journal*, 1990, Vol. 300, pp. 423-429.

Heasman, M.A., Kemp, I.W., Urquhart, J.D., and Black, R., "Childhood Leukæmia in Northern Scotland", *Lancet*, 1986, Vol. i, p. 286.

Kinlen, L., "Evidence for an Infective Cause of Childhood Leukæmia: Comparison of a Scottish New Town With Nuclear Reprocessing Sites in Britain", *Lancet*, 1988, Vol. ii, pp. 1323-1326.

Kinlen, L.J., Clarke, K., and Hudson, C., "Evidence from Population Mixing in British New Towns 1946-85 of an Infective Basis for Childhood Leukæmia", *Lancet*, 1990, Vol. 336, pp. 577-582.

Kinlen, L.J., Hudson, C.M., and Stüller, C.A., "Contacts Between Adults as Evidence for an Infective Origin of Childhood Leukæmia: An Explanation for the Excess Near Nuclear Establishments in West Berkshire?" *British Journal of Cancer*, 1991, Vol. 64, pp. 549-554.

Parkin, D.M., Stiller, C.A., Draper, G.J., Bieber, C.A., Terracini, B., and Young, J.L. (ed.), *International Incidence of Childhood Cancer*, IARC Scientific Publications, No. 87, Lyon, International Agency for Research on Cancer, 1988.

Roman, E., Beral, V., Carpenter, L. et al., "Childhood Leukæmia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in Relation to Nuclear Establishments in the Vicinity", *British Medical Journal*, 1987, Vol. 294, pp. 597-602.

Stiller, C.A., Draper, G.J., Vincent, T.J., and O'Connor, C.M., "Incidence Rates Nationally and in Administratively Defined Areas", In *The Geographical Epidemiology of Childhood Leukæmia and Non-Hodgkin Lymphomas in Great Britain 1966-83*, HMSO, London, 1991, pp. 25-35.

Urquhart, J., Palmer, M., and Cutler, J., "Cancer in Cumbria: The Windscale Connection", *Lancet*, 1984, Vol. i, pp. 597-602.

Urquhart, J.D., Black, J.D., Muirhead, M.J. et al., "Case-Control Study of Leukæmia and non-Hodgkin Lymphoma in Children in Caithness Near the Dounreay Nuclear Installation", *British Medical Journal*, 1991, Vol. 302, pp. 687-692.

CHILDHOOD LEUKEMIA IN THE VICINITY OF NUCLEAR POWER PLANTS IN GERMANY

Bernd Grosche

Head, Epidemiology and Statistics, Institute of Radiation Hygiene,
Federal Office for Radiation Protection
D–W8042 Neuherberg/Munich, Germany

1. INTRODUCTION

Within the last few years, the discussion on a possibly increased incidence of childhood leukemia in the vicinity of nuclear power plants in Germany has intensified. It started in 1978 when an increased number of leukemia deaths was reported from the vicinity of the reactor at Lingen (Kater et al., 1978). This result was disputed by another study, published in 1980. Both studies had different methodological shortcomings and will not be further mentioned in this presentation.

Another study on leukemia mortality was subsequently published by Elsasser et al., 1980. In addition to proximity to a nuclear power plant, several other possible associations were explored, including other environmental factors, e.g., natural background radiation, industrial sites. The region under study was the Bundesland of Bavaria, during the time period 1970-1978. The results of this study indicated no correlation between environmental factors and leukemia mortality.

The scope of the study was restricted to mortality, mainly due to the fact, that at the time, no data on incidence were available. In Germany, mortality data are problematic, since no local rates can be calculated. Mortality data are only available on a district level, which is not appropriate for observing effects in small areas. Moreover, the increasing success in therapy of childhood leukemia made it necessary to utilize information on incidence rather than on mortality.

In 1982, a small group headed by the author made the first attempt to gather incidence data at the community level. Again, Bavaria was chosen as the region for the study. The data were collected by counting the number of diagnosed cases in all hospitals treating leukemia. For each case, a questionnaire was completed, asking for particulars on the sex, age, and residence at time of diagnosis, and the diagnosis itself. At the end of the study useful information was obtained on leukemia incidence in children and adults up to the age of 39 (Grosche et al., 1987).

The purpose of the study was to find out whether there was an increased incidence of leukemia in the vicinity of the six reactors located in Bavaria. Two circles with the radii of 5 and 10 km, respectively, were drawn around each plant. Within the 5-km circle, the location of communities was observed separately. At the significance level of 5% an increased number of cases was observed within the 5-km circle around one reactor (Grosche et al., 1988). This finding was true for boys only. For all other regions, the number of cases observed did not statistically differ from the number of cases expected. Communities with industry and agriculture comparable to those within the 10-km circle were chosen as controls. Other environmental factors were also investigated. Increased rates were found for girls in communities with textile industry and for boys in communities with a high number of cattle, relative to human population.

In 1989, Demuth (1989) reported an increased number of leukemia cases among young people living within a radius of 20 km around the Würgassen NPP. For all other subgroups (10-, 15-, 20-, 25-km radii; 0-14, 15-20, 0-20 years of age), no statistically significant differences were detected.

In 1980, the nationwide childhood cancer registry in Mainz was founded and almost all newly-diagnosed cases among children have been reported to the registry since 1983. Data from this registry have been used in follow-up studies conducted within the umbrella of a project entitled "Radiobiological Environmental Monitoring in Bavaria" (REM).

The results of this paper are largely based upon two recently published studies on leukemia incidence in the vicinity of nuclear power plants in Germany. One of them is part of REM. The other one comprises all reactors in Western Germany. Furthermore, reference is made to two childhood leukemia clusters which have been studied extensively.

2. RESULTS FROM THE RADIOBIOLOGICAL ENVIRONMENTAL MONITORING IN BAVARIA

In 1987, a system for monitoring a number of health parameters, i.e., incidence and mortality of several diseases, was established in Bavaria. Table 1 gives an overview on the different data that are assessed in this project.

Childhood leukemia is one of the parameters assessed in this monitoring system*. As a follow-up to the results presented by Grosche et al. in 1987, the incidence of the aforementioned parameters was studied in the vicinity of nuclear reactors, five of which were under operation during the study period of 1983-1989, including the experimental Kahl nuclear power reactor (VAK), the Garching research reactor (FRM); and the Gundremmingen (KRB), Isar (KKI), and Grafenrheinfeld (KKG) commercial nuclear power plants.

TABLE 1. Health, Environmental, and Socio-Economic Information Used in REM

Health Status	Environmental Data	Socio-Economic Data
Incidence of childhood malignancies *IMSD*	Outdoor γ-radiation *BavStMDevEnvProt, Local authorities*	Socio-economic indicators *Derivate: BavStatOff, Federal Office for Employment*
Mortality of malignancies *BavStatOff*	Sulfur content in the air *BavStMDevEnvProt*	Industry *BavStatOff*
Congenial malformations *Hospitals*	Ground inversion *Meteorological Office*	Agriculture *BavStatOff*
		Population *BavStatOff*
		Migration *BavStatOff*
		Nuclear Installations *BavStMDevEnvProt*

2.1 Methods and Data

2.1.1 Methods

Statistical analysis was based upon the hypothesis that there was a difference in the occurrence of childhood leukemia between the vicinity of the reactors under study and the control regions. These two latter terms are explained as follows.

In order to define vicinity, two concentric circles having radii of 5 and 10 km respectively were drawn around each single reactor. A community is considered as belonging to one of these two circle areas, if at least two thirds of its territory was covered by the circle. Furthermore, it was noted whether the cases found within the 5-km circle occurred in well-defined areas. This was undertaken to identify those cases, resulting in an increased incidence, in one single community within the area under study.

In order to define control regions, a logistic regression analysis was carried out before comparing observed and expected cases. The regional level for this analysis is a district, mostly comprised of numerous communities. The following variables were included: gamma outdoor radiation; ground inversion; at least one community of a district belonging to the vicinity of a reactor; and urbanization of a district (derived by factor analysis from some socio-economic variables, e.g., unemployment rate).

2.1.2 Data

Leukemia cases were taken from the childhood cancer registry, which covers the whole of Western Germany (Michaelis et al., 1986). The rest of the data were obtained from different sources.

---

* Carried out by the Institute of Radiation Hygiene, funded by the Bavarian State Ministry for Regional Development and Environment Protection under contract No. 9059-743-95300.

2.2 Results

2.2.1 Regression Analysis

Urbanization proved to be the only variable which showed a significant influence on the incidence of childhood leukemia. Figure 1 shows the rates in the five categories of urbanization. Thus, control regions were defined by: same urbanization as the vicinity region; no community was located within one of the vicinity circles.

FIGURE 1. Incidence Rates in the Five Categories of Urbanization, 1983-89

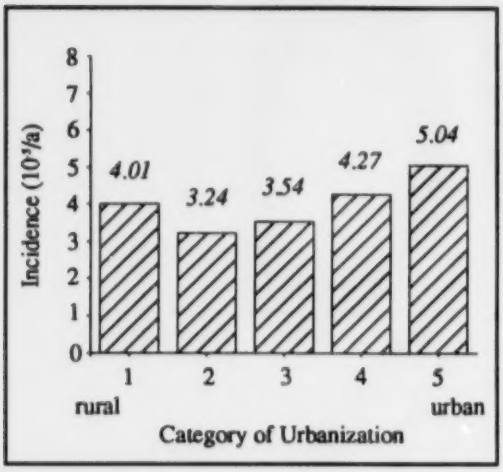


TABLE 2. O/E Ratios in the Vicinity of the Five Reactors Under Study

Plant	5-km Circle	5 to 10-km Circle	10-km Circle
VAK	3.6 (2)	3.0 (3)	3.2 (5)*
FRM	0	0.9 (2)	0.7 (2)
KRB	4.3 (1)	0	0.5 (1)
KKI	0	0	0
KKG	5.4 (2)	1.5 (6)	1.9 (8)
Pooled	2.2 (5)	1.2 (11)	1.4 (16)

* $p < 0.05$

2.2.2 Comparing Vicinity with Control Regions

Table 2 gives O/E ratios and the number of cases observed within the vicinity regions. One O/E ratio out of 15 differs significantly from 1.

An examination of regional clustering within the 5-km circle reveals that all five cases lived in communities where the reactors are located. This leads to an O/E ratio of 3.92 $[1.43;8.68]_{95\%}$.

To test whether this result is reproducible, data from a prior study were taken for comparison (Grosche et al., 1987). However, this study was based upon a different data base and direct comparison in terms of O/E ratios is not possible. Nevertheless, a comparison of the communities in which the cases occurred is reasonable and provides results as shown in Table 3.

TABLE 3. Leukemia Cases Within the 5-km Circle, 1976-1981 and 1983-1989

Plant	Study Period			
	1976-1981		1983-1987	
	5-km Circle	Comm. of Location	5-km Circle	Comm. of Location
VAK	1	0	2	2
FRM	3	1	0	0
KRB	0	0	1	1
KKI	1	1	0	0
KKG	0	0	2	2
Sum	5	2	5	5

2.3 Conclusion

Within a radius of 5 and 10 km around five reactors in Bavaria, only for one reactor and its vicinity was a difference found in the incidence compared to control regions. The finding that all cases within the inner circle occurred in those communities where the reactors were located was not reproducible when data from a prior study were used. This leads to the conclusion that the incidence within the vicinity of the reactors is comparable to that of Bavaria.

3. RESULTS FROM A NATIONWIDE INCIDENCE COMPARISON STUDY

In the beginning of this year a report was published by the cancer registry dealing with the incidence of childhood malignancies in the vicinity of all reactors located in Western Germany (Keller et al., 1992). Both vicinity and control regions were defined in a different way than in the aforementioned study. Comparable to the approach of Cook-Mozaffari et al. (1987), areas were defined as vicinity around every single reactor using circles with a radius of 15 km. Communities with at least one third of their area covered by this circle are included in the study area for this individual installation. Subregions corresponding to 5- and 10-km circles were defined in the same way.

The incidence in these areas was compared with the incidence in matched control regions. For each location of a nuclear installation, the center of a control region was determined by random selection of one community out of all districts meeting the following conditions in which:

- the smallest distance between the reference location and the district is within 30 and 100 km;
- the regional structure is the same as the reference district according to a five-class definition of the *Bundesforschungsanstalt für Landeskunde und Raumordnung;*
- the difference of population density between the two districts is not larger than 50 inhabitants/km²;
- a large proportion (60%) of cancer patients is treated in the same centres of pediatric oncology as patients from the reference district.

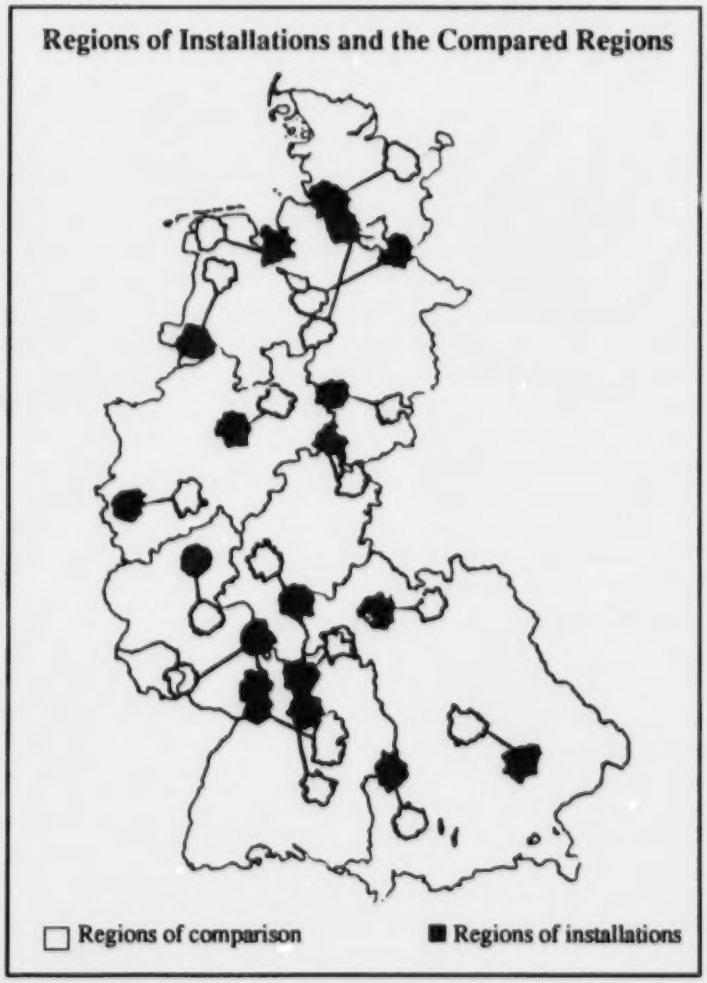
Standardized incidence ratios were calculated both for installation and control regions. This was done on the basis of the nationwide mean incidence rate. The relative risk in the location areas was derived by the expression

$$RR = \frac{SIR_I}{SIR_C}$$

Relative risks were calculated for potential sites, too. Figure 2 shows installation and corresponding control regions. Table 4 shows the results for locations and potential sites.

In addition to these ecological analyses, a questionnaire was sent to 517 of 1610 cases in all covered by the study. This questionnaire referred to possible risk factors. 427 parents received the questionnaire, 324 answered. These results were not used in the ecological analysis.

FIGURE 2. Map of Locations of Installations and Corresponding Control Areas



4. TWO SINGLE CLUSTERS

4.1 The Sittensen Cluster

In 1990, a childhood leukemia cluster was detected in the small rural community of Sittensen in Lower Saxony comprised of five cases w[illegible]ch occurred between 1987 and 1989. The age at the time of diagnosis ranged from 4 to 17 years. Since only 0.36 case was expected, this leads to an O/E ratio of 13.88 $[2;47]_{99.9\text{-CI}}$. In response to these findings, an advisory group was

TABLE 4. Relative Risks of Childhood Leukemia in the Vicinity of Nuclear Installations in Western Germany, 1980-1990.

	Time of Starting Operation														
	Before 1970			1970-1980			After 1980			All			Planned		
	SIR_I 0_I	SIR_C 0_C	RR p	SIR_I 0_I	SIR_C 0_C	RR p	SIR_I 0_I	SIR_C 0_C	RR p	SIR_I 0_I	SIR_C 0_C	RR p	SIR_I 0_I	SIR_C 0_C	RR p
Acute leukemias 0-4 years															
< 5 km	1.58	.22	7.09	.61	.63	.97	1.14	.00	—	1.26	.42	3.01	1.75	.42	4.16
	12	*1*	*.02*	*4*	*4*	*.65*	*3*	*0*	*.21*	*19*	*5*	*.02*	*6*	*5*	*.02*
< 10 km	1.03	.57	1.81	.89	.78	1.13	1.09	1.01	1.08	1.05	.88	1.18	1.07	.88	1.21
	34	*13*	*.04*	*29*	*22*	*.38*	*20*	*14*	*.48*	*82*	*48*	*.20*	*13*	*48*	*.32*
< 15 km	.96	.78	1.23	.81	.57	1.43	.97	.75	1.30	.96	.75	1.28	1.43	.75	1.91
	70	*45*	*.16*	*57*	*30*	*.07*	*28*	*19*	*.23*	*125*	*87*	*.04*	*49*	*87*	*.00*
Acute leukemias 0-14 years															
< 5 km	1.31	.58	2.25	.50	1.00	.50	1.43	.32	4.45	1.10	.76	1.44	1.23	.76	1.61
	19	*5*	*.07*	*6*	*12*	*.95*	*6*	*1*	*.13*	*30*	*17*	*.14*	*8*	*17*	*.19*
< 10 km	.96	.74	1.30	.86	.88	.98	1.02	1.05	.98	.98	.98	1.00	.95	.98	.97
	60	*32*	*.13*	*53*	*46*	*.58*	*33*	*26*	*.59*	*143*	*99*	*.52*	*22*	*99*	*.59*
< 15 km	.90	.81	1.12	.83	.75	1.10	.97	.90	1.07	.93	.88	1.06	1.25	.88	1.42
	125	*89*	*.22*	*109*	*74*	*.28*	*48*	*40*	*.41*	*274*	*190*	*.29*	*81*	*190*	*.01*

established by the government of Lower Saxony, comprised of scientists from different disciplines. Until now no reasonable explanation has been found. At least for one of these cases, there appears to be a high probability of causation due to X-ray exposure (a girl with scoliosis subjected to a high number of X-ray examinations). As far as these examinations can be reconstructed, it seems that the orthopedist did not use state of the art practices.

4.2 The Elbmarsch Cluster

While the committee was working on the Sittensen cluster, another one was identified in a small community named Elbmarsch. It is part of Lower Saxony and is located on the banks of the River Elbe, opposite to the nuclear power plant of Krümmel. Five cases of leukemia among children were observed, plus one leukemia case (which is a second primary tumor after chemotherapy) in a young man and one case of aplastic anaemia in a child. There are 1413 children living in the community. Taking the five cases of the childhood leukemia into account over a two year time period, the O/E ratio turns out to be 41.7, which is significant at any level.

The same committee working on the Sittensen cluster investigated possible reasons for the Elbmarsch cluster. Again no causative risk factor was found for all cases.

5. FUTURE STUDIES

The advisory committee recommended that a case-control study be undertaken to include all childhood leukemias which did or will occur in Lower Saxony between 1988 and 1992. The purpose is to find out whether there are typical combinations of risk factors among cases who developed their leukemia within a cluster.

This study is comparable to a nationwide case-control study investigating typical patterns of risk factors among those children who developed leukemia in the vicinity of a nuclear power plant.

Both studies will start in 1992 and will use the same protocol, based on a common pilot study, in order to permit one large meta-analysis including all cases in Germany within a given time.

REFERENCES

Bericht über die Leukämiesterblichkeit in Niedersachsen unter besonderer Berücksichtigung der Altersgruppe unter 15 Jahren. Entgegnung zur Behauptung über eine starke Zunahme von Leukämie-Sterbefälle in der Umgebung des Kernkraftwerkes Lingen, Hannover, Niedersächsisches Sozialministerium, 1980.

Cook-Mozaffari, P.J., Ashwood, F.L., Vincent, T., Forman, D., and Alderson, M., *Cancer Incidence and Mortality in the Vicinity of Nuclear Installations: England and Wales 1959-80*, London, HMSO, 1987.

Demuth, M., "Leukämiemorbidität bei Kindern und Jugendlichen in der Umgebung des Kernkraftwerkes Würgassen", Kassel, *Stattzeitung* 2, 1989.

Elsasser, U., Huber, O., and Hinz, G., *Untersuchung der Leukämiesterblichkeit in Bayern unter dem Aspekt der natürlichen und künstlichen Radioaktivität*, Berlin, Dietrich Reimer (STH-Bericht 10/1981), 1981.

Grosche, B., Hinz, G., Kaul, A., and Tsavachidis, C., *Analyse der Leukämiemorbidität in Bayern in den Jahren 1976-1981*, Neuherberg, Institut für Strahlenhygiene (ISH-Heft 73/76), 1987.

Grosche, B., Hinz, G., and Tsavachidis, C., "Leukæmia Mortality and Morbidity in Bavaria", in *Health Effects of Low Dose Ionising Radiation — Recent Advances and Their Implications: Proceedings*, London, BNES, 1988, pp. 139-144.

Kater, H., "Erhöhte Leukämie- und Krebsgefahr durch Kernkraftwerke? Kinder besonders gefährdet", *Niedersächsisches Ärzteblatt*, 1978, Vol. 20, pp. 694-695.

Keller, B., Haaf, G., Kaatsch, P., and Michaelis, J., *Untersuchung der Häufigkeit von Krebserkrankungen im Kindesalter in der Umgebung westdeutscher kerntechnischer Anlagen 1980-1990*, Mainz, Institut für Medizinische Statistik und Dokumentation der Universität.

Mainz, IMSD-Technischer Bericht, 1992.

Michaelis, J. and Kaatsch, P., "Cooperative Documentation of Childhood Malignancies in the FRG–System Design and Five-Year Results", in Riehm, H. (ed.), *Monographs in Pædiatrics*, 1986, Vol. 18, pp. 56-67.

A REVIEW OF EPIDEMIOLOGIC STUDIES OF CHILDHOOD LEUKEMIA IN CANADA

John R. McLaughlin

Senior Epidemiologist, Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard, Toronto, Ontario, Canada M4H 1A8

This overview of Canadian studies of the epidemiology of childhood leukemia includes a historical review of early studies, a summary of recent work that has been performed in Ontario, and a description of research that is currently under way across Canada. The focus of this review is on studies of the etiology of leukemia, which can employ a wide range of epidemiologic research methods. Therefore, this presentation is not limited to the formal investigation of cancer clusters because this is only one of many important and relevant epidemiologic approaches.

Epidemiologic studies of leukemia that were performed in Saskatchewan, Manitoba and Ontario during the 1960s focused on the association between socio-demographic or clinical factors and the incidence of the disease. A study performed in Quebec in the 1970s was one of the first to examine the relationship between parental occupation and the risk of cancer, including leukemia, in offspring. These historical studies will be reviewed.

Research that was recently conducted in Ontario focused on the question of whether childhood leukemia was associated with nuclear facilities. Following reports of leukemia clusters among children in the vicinity of certain nuclear facilities in the United Kingdom, Clarke et al. performed an ecologic study of childhood leukemia rates from 1950 to 1987 in five regions of Ontario within 25 kilometres of a nuclear facility. The three types of nuclear facilities that operate in Ontario include: a research and development facility; two uranium mining, milling and refining facilities; and two nuclear power generating stations. The primary aim of the Ontario study was to examine whether the leukemia mortality and incidence rates among children born to mothers residing in the vicinity of the nuclear facilities differed from the provincial average. This study was specifically designed to determine whether in Ontario there was a birth cohort phenomenon as was reported in 1987 in the region around the Sellafield nuclear fuel reprocessing plant in England. The Ontario Cancer Registry was used to identify children, aged 0-14, who died from or were diagnosed with leukemia. Overall, the observed number of leukemia deaths (O = 54) was slightly greater than expected (E = 46.1) during the period of facility operation, but the difference was within the bounds of chance variation. In the analysis of individual facilities, confidence intervals were generally wide because of the small observed and expected numbers; however, in the vicinity of a specific nuclear power generating station the observed relative excess of leukemia was close to being beyond the bounds of change variation.

In 1990, when this ecologic study was being completed, a case-control study in England was reported which showed that in the vicinity of the Sellafield nuclear fuel reprocessing plant there was a strong association between paternal occupational radiation exposure and leukemia in offspring. Subsequently, we began a case-control study in Ontario to test this hypothesis, that is, to determine whether the occurrence of childhood leukemia was associated with the occupational exposure of fathers to ionizing radiation. This study focused on the effects of exposures received during employment in the nuclear industry, particularly in the period before a child's conception. Cases where children (age 0-14) with leukemia who were born to mothers residing in the vicinity of an operating nuclear facility in Ontario from 1950 to 1988 were identified from the Ontario Cancer Registry. Eight controls per case were selected from birth certificates, and were matched by date of birth and resident at birth. A computerized record linkage was performed to identify fathers monitored by the National Dose Registry for occupational exposure to ionizing radiation. In the vicinity of five nuclear facilities in Ontario, 112 cases and 890 controls were identified. A discussion of preliminary results of this study will be presented.

A major theme of current Canadian research is the effect of exposures to environmental agents other than ionizing radiation. Currently, large scale epidemiologic studies of childhood leukemia are in progress in British Columbia and Quebec, and a large study is now beginning in Ontario. These major studies employ a case-control design and aim, in particular, to determine whether childhood leukemia is associated with electromagnetic fields, although the complete range of potential risk factors are being taken into account. Also, studies of whether the spatial distribution of leukemia is related to regional variation in environmental factors have recently been reported from Quebec and are currently under way in Ontario.

CHEMICAL EXPOSURE AND LEUKEMIA CLUSTERS

Raymond A. Cartwright

Leukæmia Research Fund Centre for Clinical Epidemiology, University of Leeds
17 Springfield Mount, Leeds LS2 9NG, U.K.

1. ABSTRACT

This paper draws attention to the heterogeneous distribution of leukemia in childhood and in adults. The topic of cluster reports and generalized clustering is addressed. These issues are applied to what is known of the risk factor for both adult and childhood leukemia. Finally, the significance of parental occupational exposure and childhood leukemia is covered.

2. INTRODUCTION

We know that many types of leukemia are distributed unusually within populations. This has been shown by recently reported analyses of mainly adult leukemia distribution (Cartwright et al., 1990) and a further one devoted to childhood leukemia (Draper, 1991) in the UK. World-wide distribution of various leukemia types apparently vary by county (Muir et al., 1987).

The significance of these international and more local variations is still obscure. Similarly, the distribution of cases at a neighbourhood level has only recently been systematically addressed using large and accurate data sets (Cartwright et al., 1990; Draper, 1991).

3. CLUSTERS

It is difficult to define the exact meaning of the emotive term "cluster", largely because it is used, often by the general public, to define a post hoc set of unusual observations, which can vary considerably in scientific credibility. It is probably more useful to perceive them as a general phenomena of "statistically unusual close case aggregations" and as such they are entirely defined by the methods used. There are several powerful methods now available and these are detailed in various publications including those by Cartwright and Draper cited above.

So far, it has emerged that childhood leukemias display a general tendency for close case aggregation, or clustering, whilst there is less certainty about other adult leukemias (Draper, 1991). Undoubtedly all leukemias rarely display post hoc evidence for large and possibly unusual clusters of cases, the significance of these within the general pattern of the clusters is uncertain.

A general tendency for clustering readily leads to hypotheses of transmissibility by infectious agents. These have some further epidemiological support from various studies (Alexander et al., 1990; Kinlen, 1988) and some convincing theoretical and biological support particularly from Professor M. Greaves (Greaves, 1988). In addition, general clustering could also be linked to genetic susceptibility within kindreds or to local environmental insults of a non-infectious nature. However, far less is known about these latter possibilities. These observations are further clouded by the obvious statistical problem (which many persons find difficult to grasp), namely that many instances of close case aggregation are entirely fortuitous. For example, some computer simulation work that accompanies certain new statistical tests of a "non-boundary" type, shows that 8% of all the cases fall within clusters, entirely by chance.

4. CHEMICALS AND LEUKEMIAS

- **Adult Diseases (AML, CML, ALL)**

- **Direct Exposure and General Population Exposure**

Chemicals are undoubtedly one of the commonest causes of adult leukemia: cigarette smoking may cause up to 30% of the diseases (McLaughlin et al., 1989) whilst chemotherapeutic drugs increase leukemia risks by several hundred fold (Kaldor et al., 1990). Significant exposures to benzene, also, result in leukemia excesses (Rinsky et al., 1987).

These latter observations and other more contentious results such as exposure to ethylene oxides (Hogstedt et al., 1986) are all based on results from heavily exposed persons or those people thought to be so exposed. It is quite

conceivable that a neighbourhood cluster of cases could be the result of workers living nearby in the vicinity of the plant and all having the same occupational exposure. Conversely, workers may originate from a neighbourhood with high leukemia rate and as they work at the same factory, appear to point to a common occupational hazard. Such an instance has been reported in a carpet factory where no known leukemogens were used (Cartwright et al., 1987).

However, non-occupationally based adult leukemia clusters have often been assumed to be related to low-dose exposures of some kind. This has led to a series of unsatisfactory investigations whereby drinking water sources (Lagakos et al., 1986) or overhead powerlines (Smith, 1992), for example, have been weakly implicated or rejected without solid statistical support or sound biological bases. Most cluster observations and investigations of adult disease tend to be under-reported and so this area has yet to be given the proper attention it deserves.

A new initiative in the UK has a sounder and systematic approach (Elliot et al., 1992) whereby all putative point sources of pollution are pooled to give a much more powerful statistical approach. This has yet to be applied to leukemia investigations, however.

5. CHILDHOOD DISEASES (ALL, AML, NHL)

• Direct exposure

The only well established chemical link between leukemia and a known substance is from the ingestion of large doses of chloramphenicol (Shu et al., 1987). It is not known if low doses or other similar drugs cause childhood leukemia. Apart from case reports, those children given chemotherapy and analyzed epidemiologically seem remarkably resistant, so far, in their lack of secondary leukemia (Hawkins et al., 1987). No investigation of childhood case clusters have ever suggested these iatrogenic substances to be responsible.

• *In utero* exposure

Despite several studies addressing this issue, there is no study or clear consensus as to any substance or exposure in pregnancy that might result in a childhood leukemia (McKinney et al., 1987), the exception being *in utero* X-ray exposures (Hawkins et al., 1987) — still a controversial area, however, due to the apparent discrepancies between dose and tissue responses.

6. PARENTAL EXPOSURE AND CHILDHOOD LEUKEMIA

By the same logic noted above, clusters of childhood leukemia might arise because the children of workers at a local factory live in the same neighbourhood. This aspect is explored elsewhere by Professor M. Gardner with respect to ionizing irradiation. However, other parental exposures have been associated with childhood leukemias — often by non-statistically significant associations. These include occupations such as farming (Bithell et al., 1975), iron and steel industry (Gardner et al., 1990) and professional sportsmen (McKinney et al., 1991). In a study in the north of England, exposure of both parents to wood dust prior to conception of the case child and exposure to some chemicals including benzene also proved a statistically significant association (Clark et al., 1985). These are controversial in that they are almost unique observations and also there is no known biological mechanism involved. Related observations include mothers exposure to leather dust (Clark et al., 1985; McDonald et al., 1986) resulting in high perinatal mortality and possibly cytogenetic abnormalities in the children and mothers exposed to textile fibre dust and ALL in children (Infante-Rivard, 1991).

7. CONCLUSIONS

The links between chemicals exposures and clusters remains to be resolved by direct exposure and fully explored as indirect exposure for both childhood and adult leukemia. Steps are afoot to investigate all such aspects further in an adult acute leukemia case-control study and in a newly set up series of studies directed to childhood leukemia.

The only way in which specific instances of unusual case distribution is explained is by the general understanding of the majority of the causes of the disease. This approach is now being followed in a number of countries.

REFERENCES

Alexander, F.E., Ricketts, T.J., McKinney, P.A., and Cartwright, R.A., "Community Lifestyle Characteristics and Risk of Acute Lymphoblastic Leukæmia in Children", *Lancet*, 1990, Vol. 336, pp. 1461-1465.

Bithell, J. et al., "Prenatal Irradiation and Childhood Malignancies", *British Journal of Cancer*, 1975, Vol. 31, pp. 271-287.

Cartwright, R.A., Miller, J.G., and Scarisbrick, D.A., "Leukæmia in a Carpet Factory: An Epidemiological Investigation", *Journal of the Society of Occupational Medicine*, 1987, Vol. 37, pp. 42-43.

Cartwright, R.A. et al., *Leukæmia and Lymphoma: An Atlas of Distribution Within Areas of England and Wales, 1984-1988*, Leukemia Research Fund, 1990.

Clark, M. et al.,"Leatherworkers: A Possible Hazard to Reproduction", *British Medical Journal*, 1985, Vol. 290, pp. 1235-1237.

Draper, G. (ed.), *The Geographical Epidemiology of Childhood Leukæmia and NHL in Great Britain 1966-83*, London, OPCS, 1991.

Elliot, P. et al., "The Small Area Health Statistics Unit", *Journal of Epidemiology and Community Health*, in press (1992).

Gardner, M. et al., "Results of a Case-Control Study of Leukæmia and Lymphoma Among Young People Near Sellafield", *British Medical Journal*, 1990, Vol. 300, pp. 423-434.

Greaves, M., "Speculation on the Cause of Childhood Acute Lymphoblastic Leukæmia", *Leukemia*, 1988, Vol. i, pp. 120-125.

Hawkins, M.M. et al., "Incidence of Second Primary Tumours Among Childhood Cancer Survivors", *British Journal of Cancer*, 1987, Vol. 56, pp. 339-347.

Hogstedt et al., "Epidemiologic Support for EthyleNeoxide as a Cancer Causing Agent", *Journal of the American Medical Association*, 1986, Vol. 255, pp. 1575-1578.

Infante-Rivard, C., "Acute Lymphoblastic Leukæmia Among Spanish Children and Mothers Occupations", *Journal of Epidemiology and Community Health*, 1991, Vol. 45, pp. 11-15.

Kaldor, J. et al., "Leukæmia Following HD", *New England Journal of Medicine*, 1989, Vol. 227, pp. 7-13.

Kinlen, L. "Evidence for an Infectious Cause of Childhood Leukæmia", *Lancet*, 1988, Vol. 332, pp. 1323-1327.

Lagakos, S.W. et al., "An Analysis of Contaminated Well Water and Health Effects on Woburn, Mass.", *Journal of the American Statistical Association*, 1986, Vol. 81, pp. 583-596.

McDonald, A.D. et al., "Outcome of Pregnancy in Leatherworkers", *British Medical Journal*, 1986, Vol. 292, pp. 979-981.

McKinney, P.A. et al., "The Interregional Epidemiological Study of Childhood Cancer", *Archives of Disease in Childhood*, 1987, Vol. 62, pp. 279-287.

McKinney, P.A. et al., "Paternal Occupations of Children with Leukæmia in West Cumbria, North Humberside and Gateshead", *British Medical Journal*, 1991, Vol. 302, pp. 681-687.

McLaughlin, J.K. et al., "Cigarette Smoking and Leukæmia", *Journal of National Cancer Institute*, 1989, Vol. 81, pp. 1262-1263.

Muir, C. et al. (ed.), *Cancer Incidence in 5 Continents*. Vol. 5, Lyon, International Agency for Research on Cancer, 1987.

Rinsky, R.A. et al., "Benzene and Leukæmia", *New England Journal of Medicine*, 1987, Vol. 316, pp. 1044-1050.

Shu, X.O. et al., "Chloramphenicol Use and Childhood Leukæmia in Shanghai", *Lancet*, 1987, Vol. ii, pp. 934-937.

Smith, A., Personal communication, 1992.

DISCUSSIONS

1. Discussion after P. Boyle's Presentation

In response to a question on the importance of sample size, P. Boyle noted that the authors were dealing with a real life situation, namely, the frequency with which children's leukemia was found in Yorkshire, where good registration procedures exist. They had a total of 350 cases to work with in looking for clusters of childhood leukemia. The sample size could be increased if they were dealing with, for example, breast cancer or lung cancer, but the current interest was in childhood leukemia.

P. Boyle had not addressed the issue of looking for excess leukemias around a point source. There is even less mathematical theory on how to address this latter issue. However, P. Boyle pointed out that at least two speakers would address the question of excess leukemias around a point source later in the symposium, and that his approach was complementary to that of Draper and of Cartwright in the U.K.

2. Discussion after J.G. Hall's Presentation

In response to a question on the logistics of identifying maternal and paternal chromosomes in a given patient, J.G. Hall noted that it was no longer terribly difficult in the laboratory. The critical item is to know which chromosome one is interested in and to obtain molecular DNA markers for that chromosome. DNA markers for both the short arm and the long arm of most chromosomes are now available. In the case of a particular chromosome, for example, one that is likely to be involved in leukemia, it is fairly easy to identify the maternal and paternal chromosomes as long as one has chromosomal DNA samples from the mother and the father of the patient as well as the patient in question.

The proposed human genome project would help to identify all human genes so one could identify the candidate genes causing leukemia. J.G. Hall's bias was that these genes will be growth factors or proto-oncogenes, which are normally under control but where loss of control leads to cancer.

In response to a question on genetic or somatic causation of leukemia, J.G. Hall noted that, to a general pediatrician, some cases appear to run in families but most cases appear to be sporadic. Nevertheless, all cases seem to be characterized by a loss of chromosomal material. In a general way, one can try to predict from the loss involved in different cases the likely outcome of that cancer. There is now a major effort to identify the particular loss of chromosomal material in each case. This knowledge is used by clinicians, who can derive from it some understanding of the natural history of that cancer, to try to define the best treatment. What has not been done up to now is to determine whether it is material from the father's chromosomes or the mother's chromosomes that has been lost. This latter question is a very crucial issue for those scientists who are looking for environmental causes of childhood cancers.

3. Discussion after C.W. Heath's Presentation

Several questions were concerned with the U.S. National Cancer Institute (NCI) study of cancers in the vicinity of nuclear facilities in the U.S.A. (see, for example, Jablon et al., "Cancer in Populations Living Near Nuclear Facilities", *Journal of the American Medical Association*, 1991, Vol. 265, pp. 1403-1408). In response to these questions, C.W. Heath noted that this NCI study included all commercial nuclear power plants that had gone into operation in the U.S.A. by 1981. This included plants that were in construction at the time of the accident at Three Mile Island. Plants that started up after 1981 were not included in the study because of considerations of latency for cancer development.

He had used the words "powerful evidence" in relation to the large size of this NCI study, and the uniformity of the nation-wide approach to the cancer data. The power of a large ecological study does not necessarily apply to decisions about any particular cluster that might be detected, such as that reported in the vicinity of a plant in Plymouth, Massachusetts. The evaluation of an individual cluster must follow other investigative lines. But this evaluation must be done against the background of the nation-wide information about relative risk of power plants as a whole. Whether one is considering nuclear power plants, toxic dumps, measles infections or other possible causes for a leukemia cluster, the collective evidence does not necessarily provide an answer for each individual cluster but must be taken into account as background in the interpretation of an individual study. That is to say, a local study that draws a conclusion that the local nuclear power plant was the cause of the leukemias under study would have to do so in the face of the national evidence that, overall, power plants do not appear to cause this type of effect very often.

An inevitable problem with the NCI study based on counties is that these counties are not all nice uniform little units. One could perhaps question the methods for selections of control counties. But it is obvious that in some cases the control counties had increased cancer rates and in other cases decreased rates. The findings were based primarily on cancer deaths. However, there was an opportunity to look at incidence data in Connecticut and Iowa, because these two states had geographically-based state-wide registries of cancer incidence. Overall, the results from the study of cancer incidence did not contradict the findings from the larger study of cancer deaths. The one county in Connecticut that stood out because of a high cancer incidence after startup of the nuclear plant also had an equally high incidence prior to the time of startup.

In response to questions about causes of the leukemia clusters that had been investigated by the Centre for Disease Control, C.W. Heath stated that he did not know of any investigation that had concluded that an individual cancer cluster was due to anything other than chance. Despite all efforts to find biologically meaningful associations, no case was made for association with other factors in the community. In other studies of clusters of disease, they had looked for association with particular schools, infectious diseases and new towns, but failed to find good evidence for these associations. The communities reported by C.W. Heath in his presentation were all instances in which an investigation had been requested. The fact that eight cases of leukemia were observed in a given location where 1.5 cases were expected is merely a way of saying yes, there are more leukemias here than expected. But C.W. Heath would not like to attach a statistical significance ("p") or biological significance ("b") to this excess in view of available data. The excess could just as easily be caused by chance, such as occurs in a random numbers table.

Telling people in a community that the cluster is due to chance is hardly the first thing that an investigator says. It is the last thing he or she says after one has done after all that seems reasonable both to the investigator and to the person(s) who requested the investigation. The client has to be made aware from the beginning that there is a possibility that a leukemia cluster might be due to chance. But we have to look as hard as we can to see if there is some other possibility. A conclusion based on these investigations is persuasive only to the extent that the investigation seems to everyone involved to have been as much as could be done reasonably. The concept of what can be done reasonably depends on how soon we get started with the investigation, how good we are at communication with people in the local community, and all those other things which are difficulties for everyone in community health practice.

4. Discussion after G.J. Draper's Presentation

In response to a question concerning children of the Japanese bomb survivors, G.J. Draper agreed that there was no evidence for an increase in childhood leukemia in the children of parents exposed to radiation at Hiroshima and Nagasaki in 1945. But it is not known what aspect of parental radiation exposure might be important. If there really is a preconception radiation effect, should we be looking at total dose prior to conception or dose in a short term prior to conception? The Gardner study says there is an association of childhood leukemia with high doses to the father within six months prior to conception. In this case, the Japanese bomb data are not really relevant because most of the children were conceived quite a long time after their fathers were irradiated.

Data from Dounreay did not confirm the Sellafield hypothesis, but the radiation doses were probably much lower. No other study in the U.K. has addressed this question yet, although we are currently looking at 100,000 radiation workers and their children in the U.K. There is no confirmatory evidence from elsewhere in the world, but it is not clear how many studies have been done.

The possibility that environmental radiation might be involved at Dounreay or Aldermaston cannot be excluded. But the environmental doses are so low that most people feel it can't be true.

It is puzzling why other genetic effects are not found, but their absence is not well-documented. To the best of G.J. Draper's knowledge no one had done any chromosome work at all on the children who developed leukemia, to see whether some of the chromosomal material from the father had been lost.

Social factors might play an important role in the vicinity of Aldermaston, but one should wait for the results of a case-control study which is currently in progress in that area. Possibly the results can be explained by the general clustering phenomenon, but that still leaves open the question as to why clusters occur in these places. The question of possible viral causation is difficult to answer.

G.J. Draper felt that he was unable to answer the question of whether most or all workers with high radiation doses from the Sellafield facility lived in Seascale, and, if not, why did the childhood leukemia cluster occur in Seascale? Seascale is a commuter village for workers from Sellafield. The place of residence of workers with high

radiation doses has not been properly resolved, and represents a possible criticism of the Gardner study. G.J. Draper did not think that anyone knew what proportion of the collective dose from the Sellafield facility was resident in Seascale.

5. Discussion after B. Grosche's Presentation

B. Grosche noted that the applicability of the Gardner hypothesis had been explored for the one clear example of a childhood leukemia cluster which was observed in Elbmarsch in Lower Saxony near a nuclear plant. One father worked at the plant but did not receive radiation exposure. The other fathers did not work at the nuclear plant. There was thus no evidence of any association with occupational radiation exposures at the plant.

In response to questions on environmental dose levels, B. Grosche noted that exposures to natural background radiation in the studied areas around nuclear facilities in Bavaria was about 100 times higher than the maximum exposures from the nuclear reactors. There was no evidence that excess leukemias occurred only downwind of the reactors. He did not think that releases from Chernobyl would have any effect on these studies because the time period of his study was 1983-89 and the Chernobyl accident occurred in 1986. One would expect a latency period of two to five years for any possible effects of Chernobyl releases on leukemia rates, and thus the releases did not seem relevant to this particular study.

In response to a question on overlap of control and vicinity regions, B. Grosche referred to a map which had been shown during his presentation. There are 20 nuclear reactors in West Germany. In general, there is no overlap either of vicinity regions or of control regions.

In as far as future studies are concerned, three studies were described by B. Grosche. Because two childhood leukemia clusters had been identified in Lower Saxony, a case-control study is starting this year to look for combinations of risk factors for those children who develop leukemia inside a cluster as compared to those who develop leukemia outside a cluster. A second case-control study will cover the whole of Germany, including the former German Democratic Republic, and look for combinations of risk factors for those children who develop leukemia in the vicinity of nuclear power plants as compared with those who develop leukemia in other areas. Both studies will use the same protocols so that the results can be combined at the end of the two studies. We will then have data relevant to almost every case of childhood leukemia occurring in Germany over a given time period. The third study of interest is concerned with biological dosimetry. A lot of blood samples will be taken to see if there are more chromosomal aberrations in children living in the vicinity of nuclear power plants compared to those living in other places.

6. Discussion after J.R. McLaughlin's Presentation

J.R. McLaughlin agreed that another approach to the question of childhood leukemia and paternal irradiation would be to look at medical X rays of fathers prior to conception of children who developed leukemia. The problem may be the logistics of identifying the data, the number of people who could be identified and the dose levels received. One of the reasons for the focus on occupational cohorts is that the doses are recorded and that these doses are probably greater than the low doses received from medical diagnostic X rays.

He did not wish to comment on the comparability of doses in the Ontario nuclear facilities with those at Sellafield until the peer review of his report on the case-control study had been completed later this year. It was noted that the name of the father of a case of childhood leukemia was taken from the birth certificate in the case-control study, and then linked to the names in the National Dose Registry. No attempt was made to identify the father by genetic markers.

The control children in the case-control study were selected in the same manner as in the Gardner study. They were identified from birth certificates and linked to the same general region and time of birth. The leukemia cases were all those identified within a region of about 50 km from the nuclear facility, which is easily within commuting distance in Ontario. No attempt was made to link the fathers of all leukemia cases in Ontario with the National Dose Registry, since most of the parents of these children would not be occupationally exposed at the nuclear facilities, which was the hypothesis that was being tested.

The case-control study was feasible, efficient and could be done with adequate scientific rigor and precision. A prospective historical study on the children of all parents listed in the National Dose Registry would require a large effort in terms of resources and time. If a nation-wide study of this kind were being considered, the experiences in the case-control study described by J.R. McLaughlin would serve as a useful starting point.

J.R. McLaughlin was dubious about the value of other methods of pooling data on childhood leukemia in the general vicinity of the five nuclear facilities in Ontario. This particular study was a general ecologic approach, with no information on emissions or occupational doses received. The potential exposures are not the same. The facilities are very different and related only in that ionizing radiation is involved. There are other statistical methods of analyzing data, accepting heterogeneity in different cells, but these are clearly irrelevant in a study of this size, where we do not have a lot of precision in the numbers. The results and conclusions from this study are not really changed if one pools data in all possible combinations.

In response to a question from a medical practitioner on where society should be directing its efforts in attempts to preventing childhood leukemia, J.R. McLaughlin stated that the majority of childhood leukemias in the province were not related to nuclear facilities. The relative risk factors for exposure to electromagnetic fields or parental radiation are relatively low and the attributable fraction of childhood leukemias in the general population will be small. We therefore need studies looking at the complete spectrum of potential risk factors. Progress is slow but is being made.

7. Discussion after R.A. Cartwright's Presentation

In response to questions on solvents and exposure to other chemical agents as potential confounders in the study of radiation-related leukemias near the Sellafield reprocessing facility, R.A. Cartwright noted that scientists in the U.K. will be taking a careful look at this possibility. No good evidence has been published yet. A wide variety of solvents and other materials are used at Sellafield, although benzene was used for only a brief period in the 1950s. Certainly this is one of the things they had thought about. But none of the other factors mentioned in R.A. Cartwright's presentation is sufficient by itself to explain the cluster of childhood leukemias near Sellafield. A first priority is to get some dosimetry on the exposure of Sellafield workers to particulates.

The age distribution for childhood leukemia does not support the concept that it is due to continued exposure to various agents, as in the case of adult lung cancer, since this should result in a steady increase in risk with age. It seems probable that the development of childhood leukemia may involve only two or three steps in metabolism, in contrast to the seven or eight steps that seem to be involved in the development of some adult cancers. The first step might be some kind of genetic susceptibility, the second might be some challenge to the immune system or some other challenge.

In response to a question on known differences in leukemia susceptibility between inbred mice strains and possible ethnic differences in genetic susceptibility to childhood leukemia, R.A. Cartwright said that U.K. scientists would clearly like to explore this question. Childhood leukemia is rare in ethnic minorities in Britain and so far they do not have any study large enough to separate out data on different ethnic groups. However, the British scientists will be collaborating with other scientists in Europe, North America and elsewhere around the world to see if any reliable information can be obtained.

CONCLUDING REMARKS

1. Judith Hall

My talk was concerned with chromosomal markers as a potential way of looking at mechanisms, which was rather different from the other presentations, but it may help to stimulate thinking about the need to find a biologically sound mechanism for cases of childhood leukemia. We live in an age where it is possible to have molecular markers to follow genes or chromosomes from one generation to another. I hope that people will keep DNA samples from identified cases of childhood leukemia and from their parents in order to be able to look at some of the mechanisms that may come to light.

It has been recognized over the last three or four years that there are a number of very clear parent-of-origin effects, that is to say, the effects of a given gene may be quite different depending on which parent has transmitted the genetic information. These effects are manifested primarily in growth, behaviour and survival. The aspect of growth and growth factors, which are proto-oncogenes which become oncogenes, is particularly important with regard to childhood cancer. From my perspective, I would hope for a study of cases found in clusters to see if there is a common biological mechanism that produces them. Theoretically, if it was due to parental exposure, one would expect to see that the DNA inherited from that parent was altered in some way. There are specific mechanisms for radiation-induced mutations which could be examined. Alternatively, some of the non-DNA changes that are involved in imprinting might be responsible.

Finally, these new mechanisms suggest an opportunity for transgenerational effects. One would be looking at exposures of the grandmother as well as the mother in the case of females and at exposures of the father in the case of males, if the genetic changes occur at meiosis.

2. Peter Boyle

A lot of effort has gone into the investigation of clusters, however, the term "cluster" may be ill-defined. A major problem is to calculate the role of chance in putting together these unusual aggregations of cases. It has been very difficult until the last five years to interpret results because of the wide variety of analytical methods used. My colleague, Dr. Freda Alexander, and I took the most recently developed analytical methods and asked the relevant people to perform an analysis in blind fashion of 50 data sets which we generated. All the methods had reasonable success in testing non-randomness, but they were quite prone to both false positive and false negative findings.

Tremendous pressure is building up in various parts of the world for public health authorities to take large data bases and trawl through them to try to identify clusters. This is an exercise which must be undertaken not only with care and attention but with an unusual level of care and attention. A lot of thought must go into methods of follow-up on the clusters or spurious clusters which will be identified in such an exercise. Statistical approaches to a data set can indicate, with some degree of error, whether or not clustering is present but cannot tell us whether this clustering is real, that is to say, whether the cases in a cluster are related to each other by some social or biological factor or have some common relationship to some other event or circumstance. There are limitations to the methodology plus extra limitations imposed by the potential for error in real data bases such as we discussed earlier today. Conclusions can be drawn, but the investigation of causes will always require further epidemiological study before the results become meaningful.

3. Bernd Grosche

I talked about leukemia in the vicinity of nuclear installations in Germany. There was little or no evidence for effects of these plants on the incidence of childhood leukemia. Two clusters of childhood leukemia in Lower Saxony, one of which is near a nuclear plant, are of interest and are under study. We now have an opportunity in these case-control studies to see if there might be some underlying combination of risk factors in children who develop leukemia within a cluster. This is a very positive result of the ongoing discussion on whether there might be leukemias caused by nuclear power plants. This discussion may also promote development of epidemiology in Germany, where the amount of expertise does not seem to be quite as high as in England and some other countries.

4. Clark Heath

These discussions have been very interesting and covered both the existence of leukemia clusters and causation. This particular symposium has, of course, focused on nuclear facilities. A major difficulty in dealing with cancer

clusters is the problem of latency, which presents a major challenge in epidemiologic studies. Until we have markers that can be applied in epidemiologic studies and clinically, I am not sure that we are going to make major progress in the study of a rare disease like childhood leukemia.

There seems to me to be three cycles in the study of leukemia clusters since 1945. My first recollection has to do with infectious diseases as possible cause, next we were talking about environment and chemicals, and now we are looking at radiation exposures as possible cause. Perhaps interest will return to infectious diseases. In that context, I was interested in suggestions in some of the English and German studies that new communities may have a different pattern of risk than older towns. I remember discussions of the same topic 20 years ago. Progress may involve a certain amount of patience.

With respect to childhood leukemia and paternal radiation dose at Sellafield, there is a difficulty related to the levels of risk and dose involved. The data do not fit the standard dose-response relationship that has been worked out from various other sources of information. If it is a real phenomenon, it does not fit in the standard genetic context, although it could perhaps be an unusual effect related to J.G. Hall's presentation.

I would view leukemia generally as a multifactorial disease where we do not know much about most of the factors involved. One of the factors which has not been sufficiently emphasized here, except by J.G. Hall, is genetic susceptibility. Having in the past studied a number of leukemia-prone families and inbred populations, the importance of genetic aspects is quite clear to me. A study of the genes involved, using molecular markers, may prove to be the key to understanding of the etiology of childhood leukemia over the next few decades.

5. John McLaughlin

I agree with many of the comments made by previous speakers and would like to stress the concept of leukemia as a multifactorial disease. It is important that future studies consider the whole combination of potential risk factors. The challenge in these studies will be to improve measurement of what actual "exposures" are. The relatively crude indicators that have been obtained through epidemiologic surveys create results that are difficult to interpret and difficult to replicate in other populations. Perhaps improving abilities in biology and in environmental measurements will enhance our ability to demonstrate exposure-response relationships.

One take-home message for me is that other epidemiologists from around the world seem to agree that formal investigation of clusters have not been very productive. Of course, we cannot ignore the significant studies that have been done. But those of us in cancer agencies have to figure out how to communicate these problems so that we can concentrate our efforts on what we feel would be productive work.

It was noted that long latency periods make it difficult to detect relationships between exposures and cancer development. Leukemia is recognized as one of the cancers with the shortest latency periods. This has permitted us to make headway in understanding some aspects, but clearly we still do not know much about the causes of the majority of cases.

Another take-home message for me is the challenge of how to start measuring things in a trans-generational perspective. Perhaps the important causes are genetic changes occurring in a previous generation including grandparents. This question presents a major challenge to an epidemiologist.

6. Raymond Cartwright

As indicated by my talk, my prejudices are towards trying to understand the generality of the reasons for childhood leukemia first, and then to return to consideration of clusters at a later stage.

7. Gerald Draper

I would like to mention five points. First, there is a methodological approach for investigating cancer incidence around nuclear installations which avoids the problem of defining these areas, whether it should be a 5-km radius or 25-km radius or whatever. A statistical analysis can be done without having to define the area. This method is currently being applied to all the nuclear installations in the U.K. and perhaps it should be applied elsewhere.

The second point is concerned with social class. The effects of social class on incidence of childhood leukemia have been shown in a number of studies, but we don't really know the reason. Is it related to one of the viroid hypotheses? We need to find out why social class has an effect on incidence of childhood leukemia.

The third point concerns Gardner's findings about the presumed relationship between childhood leukemia and pre-conception doses to fathers at Sellafield. It is not yet clear whether it is the recorded dose from external

radiation that matters or whether the same workers also had high levels of internal radionuclides or whether these workers were also exposed to high levels of organic chemicals. As R.A. Cartwright noted, there are many studies on childhood leukemia and parental occupation; however we don't really know how this fits in and chemical exposures of Sellafield workers remain as a possibility, at least, in the list of possible causes.

Fourth, someone asked about fathers exposed to medical diagnostic X rays. There are in fact two or three case-control studies published in which there was an association between childhood leukemia and paternal pre-conception medical exposures. People have looked at a lot of possible factors in case-control studies of leukemia and there have been negative findings as well, but there are a couple of studies with positive findings. I don't think that much attention would have been given to these positive findings if it had not been for the results of the Gardner study at Sellafield.

Finally, the cohort study to link the whole group of radiation workers for which there are dose records in the U.K. to registers of childhood cancer was described. The only other country in the world where this could be done seems to be Canada, and perhaps you should consider doing it.

GLOSSARY

absolute risk Expression of excess risk based on the assumption that the excess risk from radiation exposure adds to the underlying (baseline) risk by an increment dependent on dose but independent of the underlying natural risk.

absorbed dose Mean energy imparted by ionizing radiation to an irradiated medium per unit mass. Unit: gray (Gy)

ACRP Advisory Committee on Radiological Protection, Atomic Energy Control Board of Canada.

activity the number of nuclear transformations of a radioactive nuclide per unit time. Unit: becquerel (Bq)

adenosarcoma Mixed tumor which consists of a substance like embryonic connective tissue together with glandular elements.

AECB Atomic Energy Control Board of Canada.

ankylosing spondylitis Arthritis of the spine.

autosome Any ordinary paired chromosome as distinguished from a sex chromosome.

background radiation Amount of radiation to which a member of the population is exposed from natural sources, such as terrestrial radiation due to naturally occurring radionuclides in the soil, cosmic radiation originating in outer space, and naturally occurring radionuclides deposited in the human body.

baseline rate Cancer experience observed in a population in the absence of the specific agent being studied; the baseline rate might, however, include cancers from a number of other causes, such as smoking, background radiation, etc.

becquerel (Bq) Unit of activity equal to one radioactive disintegration per second.

BEIR Biological Effects of Ionizing Radiation; an advisory committee which is funded by the U.S. Environmental Protection Agency and which reports to the U.S. National Academy of Sciences.

blastomere One of the cells produced by cleavage of a fertilized ovum, forming the blastoderm.

cancer Malignant tumor of potentially unlimited growth, capable of invading surrounding tissue or spreading to other parts of the body by metastasis; some cancers are fatal while others in certain tissues such as skin and thyroid can usually be cured by medical intervention.

carcinogen Agent that may cause cancer; ionizing radiations are physical carcinogens; there are also chemical and biologic carcinogens.

carcinoma Malignant tumor (cancer) of epithelial origin.

case-control study Epidemiological study in which people with disease and a similarly composed group of people without disease are compared in terms of exposures to a putative causative agent.

chromosome One of several rod-shaped bodies in the nucleus of a cell which contain the genes or hereditary factors.

cleavage Mitotic segmentation of the fertilized ovum, the size of the zygote remaining unchanged and the cleavage cells, or blastomeres, becoming smaller and smaller with each division.

cohort study *or* follow-up study Epidemiological study in which groups of people are identified with respect to the presence or absence of exposure to a disease-causing agent and the outcomes in terms of disease rates are compared.

collective dose Sum of the individual radiation doses received by a group of person, expressed in person-sieverts.

committed dose Total dose received from a radioactive substance in the body during 50 years following the intake of this substance in the case of workers and 70 years following the intake in the case of members of the population.

confidence interval Measure of the reliability of a risk estimate; a 90% confidence interval means that nine times out of 10 the estimated risk would be within the specified interval.

congenital Existing at, and usually before birth; referring to conditions present at birth, regardless of their causation.

DDREF Factor used to derive risk estimates of low doses of low-LET radiation at low dose rates, from risk estimates calculated from data associated with large doses at high dose rates.

deterministic See non-stochastic.

detriment Mathematical expectation of individual or collective harm incurred from exposure to radiation, taking into account the probability of each type of deleterious health effect and the severity of each effect.

diploid Having two sets of chromosomes, as normally found in the somatic cells of species such as man.

dose Dose of radiation, either an absorbed dose or dose equivalent, depending on the context.

dose commitment Sum of all doses received following the release or intake of a given amount of a radioactive material, summed over a period of time extending to infinity.

dose effect (dose-response) model Mathematical formulation of the way the effect (or biological response) depends on dose.

dose equivalent Absorbed dose multiplied by a quality factor or radiation weighting factor to account for the different potential for injury of different types of radiation, where the absorbed dose is the amount of energy absorbed the body, or in an organ or tissue of the body, due to exposure to ionizing radiation, divided by the respective mass of the body, organ or tissue; a gray of absorbed dose multiplied by the appropriate quality factor or radiation weighting factor yields the dose equivalent in units of sieverts.

dose limit Legal limit on radiation dose.

dose rate Quantity of dose per unit time.

doubling dose Amount of radiation needed to double the natural incidence of a genetic or somatic anomaly.

DREF Factor used to derive risk estimates of exposure to low-LET radiation at low dose rates, from risk estimates calculated from data associated with exposures at high dose rates.

effective dose see effective dose equivalent.

effective dose equivalent Sum of the dose equivalents received by different tissues of the human body, each multiplied by the internationally recommended values of the "tissue weighting factors" assigned to each respective tissue; the weighting factor reflects the probability that a unit dose of radiation to the tissue in question will result in a cancer in the exposed person or a serious genetic disorder in the descendants of the exposed person; the sum of the weighting factors for all tissues of the body is 1.0.

embryo the developing organism from one week after conception to the end of the second month.

epidemiology Study of the determinants of the frequency of disease in man; the two main types of epidemiological studies of chronic disease are cohort (or follow-up) studies and case-control (or retrospective) studies.

equivalent dose See dose equivalent.

exposure exposure to an internal or external source of radiation, or, depending on the context, the product of the concentration of a radioactive substance in air (or the dose rate from a source of radiation) and the duration of exposure to that concentration (or dose rate)

fertilization union of male sperm and female ovum leading to the development of a new individual.

fractionation the delivery of a given total dose of radiation as several smaller doses, separated by intervals of time.

fœtus the developing youth in the human uterus after the end of the second month.

gamete one of two cells, male and female, whose union is necessary, in sexual reproduction, to initiate the development of a new individual.

gene the biologic unit of heredity, self-reproducing and located in a definite position (locus) on a particular chromosome.

genetic disorder or **disease** an inherited disease; alternatively, a serious individual deviation from the average characteristics of human populations, which requires medical attention at some time in the person's life and which is genetic or partially-genetic in origin.

gestation the period of development of the young in the uterus from the time of fertilization of the ovum.

gonad one of the primary sex glands which include the ovaries in a woman and the testes in a man.

gonosomal referring to the sex chromosomes.

gray (Gy) Special name of the unit of "absorbed dose"; (1 gray = 1 joule/kg)

haploid having a single set of chromosomes, as normally carried by a gamete.

high-LET radiation Radiation characteristic of heavy charged particles such as protons and alpha particles where the distance between ionizing events is small on the scale of a cellular nucleus.

IAEA International Atomic Energy Agency.

ICRP International Commission on Radiological Protection.

incidence *or* incidence rate the rate of occurrence of a disease within a specified period of time, often expressed as number of cases per 100,000 individuals per year.

inheritable injury Hereditary defects that are genetically transmitted from a parent to a child and which may appear amongst the children and subsequent generations of a parent whose gonads (ovaries or testes) have been exposed to radiation anytime before the conception of children.

in utero In the womb; i.e., before birth.

in vitro In culture or in the test-tube (as opposed to *in vivo*, in the living individual)

in vivo In the living organism.

ionizing radiation Radiation which is sufficiently energetic to dislodge electrons from an atom and thus to produce ions in an otherwise non-ionized gaseous medium.

latent period Period of time between exposure and expression of the disease. After exposure to a dose of radiation, there is a delay in several years (the minimum latent period) before any radiation-induced cancers are seen.

LET (linear energy transfer) Usually expressed as units of energy deposited per unit length of the track of an ionizing ray or particle.

life-span study (LSS) Life-span study of registered Japanese atomic bomb survivors.

life table Table showing the number of persons who, of a given number born or living at a specified age, live to attain successive higher ages, together with the numbers who die in each age interval.

linear energy transfer (LET) Average amount of energy lost per unit track length.

low-LET radiation Radiations such as X or gamma rays where the distance between ionizing events is large on the scale of a cellular nucleus.

linear model *or* linear dose-effect relationship Expresses the effect (e.g., mutation or cancer) as a direct (linear) function of dose.

linear-quadratic model *or* linear-quadratic dose-effect relationship Expresses the effect (e.g., mutation or cancer) as partly directly proportional to the dose (linear term) and partly proportional to the square of the dose (quadratic term); the linear term will predominate at lower doses, the quadratic term at higher doses.

lymphoma General term applied to any neoplastic disorder of the lymphoid tissue.

mitosis Method of division of a cell, consisting of a complex of various processes, by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes characteristic of the somatic cells of the species.

morphogenesis Evolution and development of form, as the development of the shape of a particular organ or part of the body.

mortality (rate) Rate to which people die from a disease, e.g., a specific type of cancer, often expressed as number of deaths per 100,000 per year.

NCRP National Council on Radiation Protection and Measurements, USA.

neoplasms Any new and abnormal growth, such as a tumor; neoplastic disease refers to any disease that forms tumors, whether malignant or benign.

non-stochastic effects Effects whose severity is frequently a function of dose and for which doses above some threshold dose is required.

NRPB National Radiological Protection Board, UK.

nuclear facility Nuclear reactor, a sub-critical nuclear reactor, a particle accelerator, a uranium or thorium mine or mill, a plant for the separation, processing, reprocessing or fabrication or fissionable substances, a plant for the production of deuterium or deuterium compounds, and a facility for the disposal of prescribed substances, including all land, buildings and equipment that are connected or associated with such reactor, accelerator, plant or facility.

neutron Uncharged subatomic particle capable of producing ionizing radiations as an indirect consequence of its collisions with atomic nuclei.

occupational accidents Fatal or non-fatal injuries to workers which occur at work.

occupational dose *or* occupational exposure Radiation dose or an exposure to radiation received while employed as a radiation worker.

organ Structure of the body such as the lungs, gonads or thyroid gland that performs some specialized function.

organogenesis Origin and development of body organs.

ovum Female reproductive cell which, after fertilization, develops into a zygote.

perinatal Pertaining to or occurring in the period shortly before or after birth.

person-sievert (p-Sv) Unit of population exposure obtained by summing individual dose equivalent values for all people in the exposed population; the unit of collective dose

person-years-at-risk (PYAR) Number of persons exposed multiplied by the number of years after exposure.

prevalence Number of cases of a disease in existence at a given time per unit population, usually 100,000 persons.

projection model Mathematical model that simultaneously describes the excess cancer risk at different levels of some factor such as dose, time after exposure, or baseline level of risk, in terms of a parametric function of that factor; it becomes a projection model when data in a particular range of observations is used to assign values to the parameters in order to estimate (or project) excess risk for factor values outside that range.

promoter Agent which is not by itself carcinogenic, but which can amplify the effect of a true carcinogen by increasing the probability of late-stage cellular changes needed to complete the carcinogenic process.

quadratic-dose model Model which assumes that the excess risk is proportional to the square of the dose.

quality factor (Q) LET dependent factor by which absorbed doses are multi-plied to obtain (for radiation protection purposes) a quantity which corresponds more closely to the degree of biological effect produced by X rays or low-energy gamma rays; dose in grays x quality factor (Q) = dose equivalent in sieverts.

radiation weighting factor See quality factor.

radiogenic Caused by radiation.

radiosensitivity Relative susceptibility of cells, tissues, organs, and organisms to the injurious action of radiation; radiosensitivity and its antonym, radioresistance, are used in a comparative sense rather than an absolute one.

relative biological effectiveness (RBE) Biological potency of one radiation as compared with another to produce the same biological endpoint; it is numerically equal to the inverse of the ratio of absorbed doses of the two radiations required to produce equal biological effect; the reference radiation is often 200 kV X rays.

relative risk Expression of excess risk relative to the underlying (baseline) risk; if the excess equals the baseline risk the relative risk is 2.

RERF Radiation Effects Research Foundation; a bi-nationally funded Japanese foundation chartered by the Japanese Welfare Ministry under an agreement between the U.S.A. and Japan; the RERF is the successor to the ABCC (Atomic Bomb Casualty Commission)

risk coefficient Increase in the annual incidence or mortality rate per unit dose (1) absolute risk coefficient is the observed minus the expected number of cases per person year at risk for a unit dose; (2) the relative-risk coefficient is the fractional increase in the baseline incidence or mortality rate for a unit dose.

risk estimate Number of cases (or deaths) that are projected to occur in a specified exposed population per unit dose for a specified exposure regime and expression period; number of cases per person-gray or, for radon, the number of cases per person cumulative working-level month.

sarcoma Malignant growth arising in tissue of mesodermal origin (connective tissue, bone, cartilage or striated muscle)

sex-linked mutation *or* X-linked Mutation associated with the X chromosome. It will usually only manifest its effect in males (who have only a single X chromosome).

sievert (Sv) Unit of dose equivalent and o effective dose equivalent.

spermatozoon Mature male germ, the specific output of the testes.

standard mortality ratio (SMR) Standard mortality ratio is the ratio of the disease or accident mortality rate in a certain specific population compared with that in a standard population; if the ratio is based on 100 percent for the reference standard, an SMR of 200 means that the test population has twice the mortality from that particular cause of death.

stochastic effects Biological effects that may occur at random amongst an exposed group of people, with the probability of occurrence being proportional to the effective dose equivalent, usually without a threshold; cancer and inheritable injury are the stochastic effects of primary concern.

teratogen Agent or factor that causes the production of physical defects in the developing embryo.

threshold dose Minimum dose below which there is no given biological response or effect.

tissue Group of similar cells which together perform certain specialized functions (e.g., bond marrow, bone surfaces, and eye lenses)

tissue weighting factor Factor by which the dose equivalent received by any organ or tissue of the body is multiplied in order to account for the risk of fatal cancer or inheritable injury resulting from irradiation of that organ or tissue compared to the total risk of such stochastic effects resulting from the receipt of an equal dose equivalent by the whole body.

UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation.

WHO World Health Organization.

X ray Electromagnetic radiation emitted during certain rearrangements of the electron shells of an atom; X rays may be produced during radioactive decay or from the slowing down of fast electrons in any material; they are usually obtained from X-ray machines in which a metallic target is bombarded with fast electrons in a vacuum.

zygote Cell resulting from the fusion of two gametes; the fertilized ovum.

SYMPOSIUM ON LEUKEMIA CLUSTERING

Ottawa, Canada

March 11, 1992

LIST OF PARTICIPANTS

Arsenault, Benoit	Montreal, Que., Canada
Arsenault, André	Montreal, Que., Canada
Ashmore, Patrick	Ottawa, Ont., Canada
Asrad, Roda F.	Montreal, Que., Canada
Asselin, Chantal	Montreal, Que., Canada
Atchison, R.J.	Ottawa, Ont., Canada
Bailey, R.J.	Toronto, Ont., Canada
Baker, Ernie	Weston, Ont., Canada
Blanchette, J.	Ste Foy, Que., Canada
Boyd, Frederick C.	Kanata, Ont., Canada
Boyle, Peter	Milan, Italy
Brown, L.D.	Regina, Sask., Canada
Burnham, Peter Roy	Bowmanville, Ont., Canada
Callary, Eva	Ottawa, Ont., Canada
Carlisle, Sara	Chalk River, Ont., Canada
Carpenter, Maureen	Ottawa, Ont., Canada
Cartwright, Raymond A.	Leeds, U.K.
Catton, Gordon	Ottawa, Ont., Canada
Chamberlain, M. J.	London, Ont., Canada
Chatterjee, Robi	Ottawa, Ont., Canada
Ching, Shek H.	Ottawa, Ont., Canada
Choubal, Sunil D.	Saskatoon, Sask., Canada
Clarke, Aileen	Toronto, Ont., Canada
Copes, Raymond	Victoria, B.C., Canada
Cradduck, Trevor	London, Ont., Canada
Davidson, Claudette	Ottawa, Ont., Canada
Davies, Keith	Fredericton, N.B., Canada
De Winter, Denis	Saskatoon, Sask., Canada
Decaire, Richard	Montreal, Que., Canada
Dequehen, Ella	Rosemeath, Ont., Canada
Dixon, Robert	Ottawa, Ont., Canada
Doerffer, K.	Chalk River, Ont., Canada
Draper, Gerald	Oxford, U.K.
Droll, Randy	Ottawa, Ont., Canada
Duncan, R.M.	Ottawa, Ont., Canada
Duport, Philippe	Ottawa, Ont., Canada
Dvorak, Pavel	Nepean, Ont., Canada
Eaton, Roger	Nepean, Ont., Canada
Elaguppillai, V.	Ottawa, Ont., Canada
Fair, Martha	Ottawa, Ont., Canada
Farzad, Fatemah	Ottawa, Ont., Canada
Fidler, Anne	Cincinnati, Ohio, U.S.A
Finkelstein, M.	Toronto, Ont., Canada
Fyfe, M.	Ottawa, Ont., Canada
Gaudette, L.	Ottawa, Ont., Canada
Giffin, Scott	Saint John, N.B., Canada
Gordon, Karin L.	Winnipeg, Man., Canada
Goulet, Daniel	Montreal, Que., Canada
Grant, John	Toronto, Ont., Canada
Gray, Barbara	Pinawa, Man., Canada
Green, Lois M.	Toronto, Ont., Canada
Greenstock, Clive	Chalk River, Ont., Canada
Grey, Michael	Kanata, Ont., Canada
Groshe, Bernd	Munich, Germany
Guest, Alan	Toronto, Ont., Canada
Hall, Judith	Vancouver, B.C., Canada
Harvie, Jim	Ottawa, Ont., Canada
Hawkins, R.J.	Pinawa, Man., Canada
Haynes, Robert H.	North York, Ont., Canada
Heath, Clark	Atlanta, Georgia, U.S.A
Heinmiller, Bruce	Chalk River, Ont., Canada
Hill, Gerry	Ottawa, Ont., Canada
Hollins, J.	Hull, Que., Canada
Horvath, Frank	Ottawa, Ont., Canada
Irwin, Robert E.	Ottawa, Ont., Canada
Jack, George	Ottawa, Ont., Canada
Jaferi, Mike	Ottawa, Ont., Canada
Johnson, Ken	Ottawa, Ont., Canada
Jovanovich, Jovan	Winnipeg, Man., Canada
Kelly, J.W.	Montreal, Que., Canada
Khan, Arif	Pickering, Ont., Canada
King, Will	Toronto, Ont., Canada
Kramer, Gary H.	Ottawa, Ont., Canada
Krewski, Dan	Ottawa, Ont., Canada
Krishnan, V.S.	Mississauga, Ont., Canada
Kudo, Akira	Ottawa, Ont., Canada
Kupca, Stefan	Ottawa, Ont., Canada
Laberge, Solange	Montreal, Que., Canada
Lamothe, E.S.	Chalk River, Ont., Canada
Lapierre, Louis	Hull, Que., Canada
Lavoie, Christian	Ottawa, Ont., Canada
Légaré, Michèle	Ottawa, Ont., Canada
Lehnert, Shirley M.	Montreal, Que., Canada
Lentle, Brian C.	Vancouver, B.C., Canada
Létourneau, Carmel	Ottawa, Ont., Canada
Létourneau, E.G.	Ottawa, Ont., Canada
Lévesque, R.J.A.	Ottawa, Ont., Canada
Levy, Isra	Ottawa, Ont., Canada
Limson-Zamora, M.	Ottawa, Ont., Canada
Lind, Niels C.	Victoria, B.C., Canada

Lowe, Leo	Richmond Hill, Ont., Canada
Lupien, Marc	Ottawa, Ont., Canada
Macdougall, Shane	Kanata, Ont., Canada
Mao, Y.	Ottawa, Ont., Canada
Marahaj, Harri	Ottawa, Ont., Canada
Marchildon, Pierre	Ottawa, Ont., Canada
Marko, Arthur	Deep River, Ont., Canada
Marshall, Heather	Ottawa, Ont., Canada
Martin, John	St. John's, Nfld., Canada
McEwen, John	Hull, Que., Canada
McFadden, Robert	Weston, Ont., Canada
McKean, Doug	Toronto, Ont., Canada
McLaughlin, John R.	Toronto, Ont., Canada
McLean, J.R.	Ottawa, Ont., Canada
McNeill, Kenneth	Toronto, Ont., Canada
Measures, Mary P.	Ottawa, Ont., Canada
Metcalfe, Doug	Ottawa, Ont., Canada
Meyerhof, Dorothy P.	Ottawa, Ont., Canada
Michalko, Jerry	Kanata, Ont., Canada
Miller, Doris	Ottawa, Ont., Canada
Moloughney, B.	Ottawa, Ont., Canada.
Morris, Martha	Boston, Mass., U.S.A
Morrison, Donald P.	Chalk River, Ont., Canada
Mourad, Raphael	Mississauga, Ont., Canada
Muldoon, L.	Ottawa, Ont., Canada
Mustard, C.	Ottawa, Ont., Canada
Myers, David K.	Pembroke, Ont., Canada
Nowak, Major Rudy	Ottawa, Ont., Canada
Nowak, Mike	Pickering, Ont., Canada
Osborne, Richard	Chalk River, Ont., Canada
Ouellette, Gail	Montreal, Que., Canada
Pepin, Lt. (N) J.G.	Ottawa, Ont., Canada
Pfaff, James	Toronto, Ont., Canada
Phillips, Brian	Vancouver, B.C., Canada
Plante, Michel	Montreal, Que., Canada
Pless, R.	Ottawa, Ont., Canada
Poirier, Georges	Ottawa, Ont., Canada
Pomroy, Chris T. G.	Ottawa, Ont., Canada
Poulin, Maurice	Trois-Rivières, Que., Canada
Raaphorst, Peter G.	Ottawa, Ont., Canada
Rabin, Eric	Ottawa, Ont., Canada
Raman, S.	Ottawa, Ont., Canada
Redekop, Ted	Winnipeg, Man., Canada
Reese, Lionel	Hull, Que., Canada
Reiser, G.	Ottawa, Ont., Canada
Renaud, Louis	Montreal, Que., Canada
Rhéaume, Michel	Gentilly, Que., Canada
Richman, A.	Ottawa, Ont., Canada
Scott, Carol	Toronto, Ont., Canada
Shoukri, Mohamed	Guelph, Ont., Canada
Shultz, Ken	Ottawa, Ont., Canada
Smith, A.I.	Ottawa, Ont., Canada
Smith, Lesbia	Toronto, Ont., Canada
Sont, Willem	Ottawa, Ont., Canada
Spasoff, R.	Ottawa, Ont., Canada
Stocker, Harold	Ottawa, Ont., Canada
Tai-Pow, John	Weston, Ont., Canada
Takala, John M.	Saskatoon, Sask., Canada
Tamm, Judy	Pinawa, Man., Canada
Tepper, Lt. Col. M.L.	Ottawa, Ont., Canada
TerMarsch, Donna	Ottawa, Ont., Canada
Thériault, Bertrand	Ottawa, Ont., Canada
Thorson, Ian M.	Vancouver, B.C., Canada
Toms, David	Charlottetown, P.E.I., Canada
Tracy, Bliss	Ottawa, Ont., Canada
Truong, Liliane	Ottawa, Ont., Canada
Utting, Rod	Ottawa, Ont., Canada
Vasudev, Pat	Hull, Que., Canada
Waddington, John	Ottawa, Ont., Canada
Waker, A.J.	Chalk River, Ont., Canada
Watler, Donald	Yorkton, Sask., Canada
Werner, Mary M.	Ottawa, Ont., Canada
Whillans, David	Pickering, Ont., Canada
White, Mike	Ottawa, Ont., Canada
Whitlock, Jeremy J.	Hamilton, Ont., Canada
Wilkinson, Diane	Ottawa, Ont., Canada
Williams, Eric Lyn	Tiverton, Ont., Canada
Williams, Norm L.	Peterborough, Ont., Canada
Wills, Michael	Toronto, Ont., Canada
Wilson, Ian	Toronto, Ont., Canada
Wilson, Robert	Pickering, Ont., Canada
Wise, Paul	Ottawa, Ont., Canada
Wong, Tom	Toronto, Ont., Canada
Woodruff, Gary	Tulsa, Oklahoma, USA
Zangwill, Linda	Waterloo, Ont., Canada
Zielinski, Jan	Ottawa, Ont., Canada
Zikovsky, L.	Montreal, Que., Canada